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DISCUSSION ON THE LEISHMAN-DONOVAN BODY

W.B.Leishman

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corroborate Sir Patrick Manson's statement that the malarial *Anopheles* can be introduced into places where it never existed before, as in Mauritius, for instance, where in 1867 it was brought over probably from India or Madagascar. Malarial fever now is endemic in that island. Why the malarial *Anopheles* had not made its introduction before, seeing that immigration of coolies from India had existed for a score of years anteriorly, and there had been constant communication with Madagascar, whence bullocks for the market are brought —why, I say, the malarial *Anopheles* had not propagated itself in larger numbers before 1867 in Mauritius is until to-day a subject of discussion (*vide* my Notes on Malarial Fever in Mauritius, August, 1890). There is no doubt that before 1867 sporadic cases of malarial fever were known in Mauritius. During my visit to the island of Mauritius in 1899 I came across several Indians suffering from filariasis, and in most of them I traced the cause to eating the watercress growing in ponds of stagnant water. Evidently the eggs of the filaria had been deposited on the under surface of the leaves of the watercress. In Madagascar (Nossi Bé), which I also visited, where filariasis is common, the remedy is aq. chloroformi (*B.P.*), ℥j, two or three times in the two hours, until patients fall asleep; then the symptoms begin to disappear.

XIV.—W. J. SIMPSON, M.D.Aberd., F.R.C.P.,
Professor of Hygiene, King's College, London; Lecturer in Tropical Hygiene, London School of Tropical Medicine.

PROFESSOR SIMPSON remarked that the only observation he had to make was that he regretted that the experiment against malaria had been made at Mian Mir. It was not under conditions that were likely to be successful. Only a small portion of the cantonment was dealt with instead of the whole, which after all only covered an area of four miles. If a proper and efficient organization had been used over the whole cantonment probably the results would have been very different. The Government of India were well known to expect their medical officers to make bricks without straw. Other experiments were proposed to be made in the central provinces. The Sanitary Commissioner proposed that the civil surgeons of five municipalities should carry out a campaign against the mosquitos. The civil surgeons were to search out for the localities in which the *Anopheles* reproduced themselves, to take measures for the destruction of the mosquitos, and to note the results in their annual reports. Now, at the Indian Medical Congress held in Calcutta in 1894 he (Dr. Simpson) had shown that it was perfectly impossible for a civil surgeon to carry out any sanitary duties, his work in other directions being so overwhelmingly great. He had to visit the gaol and attend to the prisoners, also the lunatic asylum and the hospital, to superintend vaccination, besides performing many other governmental duties, as well as those of medical attendant to the civil servants and others of his district. No civil surgeon had any time to carry out any malarial campaign, and it was hoped that no such experiment would be attempted, for it would only lead to confusion and to failure. Nothing of this kind could be effected without a proper sanitary organization, which India was without at the present moment, but which he hoped, for the sake of the welfare of the Indian population, would be soon created.

XV.—ALEXANDER CROMBIE, M.D.,
President of the Section.

THE PRESIDENT said: We have now before us two great object lessons. Not to speak of the brilliant results which are reported from Havana, we have the success which followed the measures taken at Ismailia, which have made it a mosquito free and malaria-free sanatorium, and we have the equally signal failure of those carried out at Mian Mir, and which have failed to mitigate in the smallest degree the incidence of malaria in that cantonment, and it behoves us to ask ourselves why the same or similar measures for the destruction of mosquitos were successful at one place and failed at the other. The answer is not difficult to find. At Ismailia the means adopted were adequate, were carried out in a whole-hearted way, were applied to the whole and every part of the town, and included the adjoining marshes. Not only was the usual anti-mosquito campaign carried out in the town, but the neighbouring marshes were drained, and their stagnant water converted into running streams. The whole area was rendered unfavourable for the propagation of mosquitos. At Mian Mir, on the other hand, only a small fraction of the area was brought into the field of operations; only one corner of the cantonment was treated, and the remaining three-fourths of the area was left untouched, with its network of irrigation canals, its irrigated crops up to the very doors of the bungalows, a very paradise for the breeding of mosquitos, its pools of standing water after each shower, and no adequate provision was made to prevent the influx of *Anopheles* from outside, of larvae in the water of the canals, and of adults from the irrigated fields outside and inside the limits of the cantonment. An experiment conducted on that scale was doomed to failure. Would it have succeeded at Ismailia if the measures had been restricted to one quarter of the town, and nothing been done to prevent the immigration of *Anopheles* from the adjoining marshes? I think we may say that if the measures advocated by Ross at Ismailia had been carried out in the same partial and half-hearted way the failure there would have been just as complete as it has been at Mian Mir. Another thing has come out of the discussion, and that is the astounding fact that in the year of grace 1904 the cultivation of crops for which irrigation is essential is permitted within the limits of a cantonment for British troops. The danger to health of the cultivation of rice and other crops requiring irrigation and standing water has been recognized from all time. I was lately reading a book (*Epidemiologia Española*), published at Madrid in 1802, in which the following passage occurs: "The cultivation of this plant (rice) has often been considered contrary to public heath. From the year 1324, little more than a century after the conquest of the Kingdom of Valencia, we meet with the prohibition of the growth of rice in the neighbourhood of the capital, and in that of some of the surrounding towns. This prohibition was repeated by the same sovereign, Don Pedro the Second, in 1386, by King Don Martin in 1403, and by Don Alonso in 1483." In the memoirs of the Royal Academy of Medicine of Madrid, printed in 1797, are some excellent observations "on the cultivation of rice in the Kingdom of Valencia, and its influence on public health," by Don Antonio Josef Cabanilles. He attributes the unhealthiness of regions where rice is grown to the multitudes of insects which are produced in these marshy situations, leaving there their excrement and dead bodies, and points out that the colour of men dwelling in these regions is changed, and tertians manifest themselves, which with time augment in strength and malignancy. He insists on the prohibition of the cultivation of rice and the drainage of the fields where it is grown as the remedial measures indicated. And yet we have, six hundred years after the royal edicts I have alluded to, the all but incredible fact that the cultivation of rice and other irrigated crops is permitted inside a British cantonment. I do not think that Colonel McLeod was quite fair to Captain Sewell in this respect. That officer does not demand the abolition of irrigation throughout the length and breadth of India, but he advocates its abolition only within the limits of Mian Mir, and I think we must all agree with him that there can be no diminution of the prevalence of malaria, or of the inefficiency which it causes among the troops stationed there till it is abolished. One of two things must be done; either the irrigation system which now exists must be swept away, or the cantonment of Mian Mir must be removed to a more healthy situation. The result of the anti-malarial experiment carried out in that cantonment shows conclusively that half measures are futile.

DISCUSSION ON THE LEISHMAN-DONOVAN BODY.

I.—W. B. LEISHMAN, Major, Royal Army Medical Corps,
Professor of Pathology, Royal Army Medical College, London.

IN opening this discussion on the nature and significance of the new parasitic bodies, I would wish, in the first place, to express my sense of the honour which I feel has been done me in my having been asked to undertake it.

As this is the first meeting of the Association at which these bodies have formed a subject of discussion, it may, I think, be of most service to the members if I describe, as briefly as possible, the main facts which have been brought to light in connexion with these parasites before entering, at somewhat greater length, upon the more debateable points in connexion with their nature and significance. The blanks in our knowledge are many, but good progress has of late been made in filling in some of these, and I trust that still further additions may be the fruit of this discussion.

Since the bodies were first brought to notice quite a large

number of cases have been put on record by Donovan, Marchand and Ledingham, Manson and Low, Bentley, Rogers, and others, and it is becoming more and more evident that the disease associated with their presence is by no means uncommon in tropical countries, and there can be little doubt that, as the parasites themselves and the methods necessary for their demonstration become better known, we shall hear of many more cases.

Detailed descriptions and figures of the bodies have been published in connexion with so many of these cases that I do not propose to occupy your time upon this point, more especially as there is a general uniformity in these descriptions which leaves little doubt that the appearance of the parasites met with in the different cases is constant and regular.

Geographical Distribution.

On this point we have a certain amount of information, but cases have been reported from countries so widely apart that it would be rash at this stage to attempt to assign geographical limits to the disease. The first case in which the parasites were found was that of a soldier, invalided from Dum-Dum in 1900 with tropical cachexia and splenomegaly, and soldiers at Netley presenting a similar clinical picture were so frequently found to have served in or near this station that I termed the condition "Dum-Dum fever." Such a name was, however, only intended as a temporary expedient for the avoidance of a periphrasis in speaking of the condition with which the bodies were associated, and, as it appears likely that the disease may prove to be identical with kala-azar, this well-known name will probably be adopted.

Up to the present moment cases have been reported from three or four widely separated districts of India, from China, Tunis, Algiers, Arabia and Egypt. As our knowledge of these endemic areas is added to, it would be of great interest to endeavour to find out any physical peculiarities they may possess in common, as this may help us in the search for the alternative host which the analogy of malaria and other protozoal diseases would suggest to be necessary.

Distribution of the Parasites in the Body.

Originally found in the spleen, the parasites have since been met with in the liver, the mesenteric glands, the bone marrow, the kidney, and in ulcers involving the intestinal mucosa. The great majority of those who have searched for them in the peripheral blood have failed to detect them, but M. Laveran is of the opinion that certain small bodies occurring in the red corpuscles in some of his specimens are young forms of the parasite.

The most exhaustive accounts of the distribution of the parasites are those of Marchand and Ledingham and of Christophers, and their results are in many respects in marked agreement. According to these and other observers the parasites appear to be chiefly, if not solely, intracellular, and are met with in the protoplasm of large mononuclear cells, which are probably, as Christophers suggests, "macrophages," and of the same nature as those large phagocytes which, in malarial cases, are filled with ingested melanin granules. A fact which has been noted, and which appears to me significant, is that neither the parasites nor the cells which harbour them appear to suffer from their mutual association.

In specimens obtained by splenic or hepatic puncture during life the parasites are, however, usually found free or in groups of several members, and such free or agglomerated parasites are frequently seen to be embedded in a structureless matrix or stroma, staining grey or pale blue with Romanowsky's method. This stroma or matrix is of importance, as it is largely owing to the different conceptions as to its origin that different views have been taken as to the nature of the parasite. That the true origin of this stroma lies in the disintegration of those large mononuclear cells through mechanical violence, and that the stroma represents a fragment of the protoplasm of one of those host cells, appears probable from the work of Christophers and of Marchand, which I have been able to confirm to a large extent by the chromatin staining of sections from one of my own cases.

Symptomatology.

As I trust we shall receive fresh information on this point from some of those who are to follow me, I shall only enumerate the chief points which appear to be presented in common by the cases I have myself observed and those which have been recorded by others.

1. Splenic and hepatic enlargement—the former being apparently constant, while the latter is common but not invariable.

2. A peculiar earthy pallor of the skin, and, in the advanced stages, an intense degree of emaciation and muscular atrophy.

3. A long-continued, irregularly remittent fever, of no definite type, lasting frequently for many months, with or without remissions.

4. Haemorrhages, such as epistaxis, bleeding from the gums, subcutaneous haemorrhages or purpuric eruptions.

5. Transitory oedemas of various regions or of the limbs.

6. Complications, such as congestion of the lungs, diarrhoea and dysentery, have been frequently reported, and are occasionally the immediate cause of death.

7. Blood count. The cases coming under my own notice have shown a marked mononuclear increase, an interesting point, if confirmed by further experience, in view of the proved absence of malaria.

To these positive signs may be added certain negative ones of hardly less importance: First, the absence of malaria, except as a concurrent affection, which yields to appropriate treatment; secondly, the negative result of the agglutination test to typhoid and Malta fever; and, thirdly, the resistance to medication, and especially to quinine—at all events, in the later stages of the disease.

Relation to Kala-azar.

It will be noticed that the symptoms detailed above are very similar to those of kala-azar, a disease which has furnished matter for discussion at previous meetings of this Section, and concerning whose causation great differences of opinion have existed. I suggested in my original communication that search should be made for these bodies in kala-azar, and Bentley has since reported finding them in the spleen in cases of this disease, while his results have been confirmed more recently by Rogers. It is, perhaps, too early to say definitely that they are the cause of kala-azar, but it certainly looks as though this were the case, as they seem to occur constantly in this disease. If it should be so, the question arises whether the other cases in which the parasites have been found are identical with kala-azar, and, if this identity is proved, we must then admit that the geographical distribution of kala-azar is much wider than has been supposed, and, further, that it is not uncommon amongst Europeans.

The Nature of the Parasite.

On this point, so important for the solution of many of the unsolved problems in connexion with the disease, there has been a divergence of opinion, and it is much to be hoped that the question will soon be definitely settled. When it is, analogy should help us in clearing up the rest of the life history of the parasite, and put us on the track to what should be our ultimate goal—the prevention and, if possible, the stamping out of the disease. Stated briefly, the views that have been enunciated are the following:

1. Major Ross, working with films sent to him by Donovan, came to the conclusion that the bodies represented a new genus, belonging to the sporozoa, which he did me the honour to name Leishmania.

2. M. Laveran, also working with films from Donovan's cases, pronounced the bodies to belong to the piroplasmata, and gave them the name P. Donovani.

3. In my own opinion they appeared to represent a stage in the life-history of a flagellate organism, closely resembling a trypanosoma, if not actually belonging to that genus.

Few of those who have recorded cases of the disease have expressed their views upon this question of their nature, but Marchand and Ledingham, as a result of the study of their case, have come to the same conclusion as myself.

To examine these views more in detail: first, M. Laveran's view, that they are a species of piroplasma—a parasite of the red blood corpuscles—has met with little support from other observers, whose most careful search has failed to demonstrate their presence in the red cells of the peripheral circulation, while, further, it has been pointed out that the arrangement of the chromatin, the method of apparent multiplication, and the tendency to occur in the protoplasm of the large mononuclear cells of the spleen and liver further militate against this theory.

Such high authorities as Manson, Ross, and Marchand have also pronounced against this view. When the parasites are very numerous in a film it must happen at times that

some are superimposed on the red cells, and when this occurs it is no easy matter to say whether it is a case of a true inclusion or not. But, in addition, Laveran has found pyriform bodies recalling the shape of piroplasma bigeminum, and he further regards the pale, grey-staining stroma, frequently seen surrounding the bodies, as representing the degenerated remains of the red corpuscle which harboured the parasite. A more probable explanation of this stroma appears to be that of Christophers, to which I have already alluded.

In a later publication Laveran reports that he has met with small intracorpuscular bodies in some of Donovan's films, taken from the peripheral blood of patients in whose spleens the parasites had been detected by spleno-puncture. These bodies Laveran considers as young forms of the piroplasma, and he mentions a series of points in which they appeared to him to differ from young malarial parasites. So far as I am aware, this observation has not yet been confirmed.

Secondly, in Major Ross's view we have to deal with a representative of a new genus of the sporozoa, and he regarded "the individual bodies as spores produced in the matrices, which would appear to be relics of the parent organism." In this connexion it may be noted that the parasites found by Wright in a Delhi boil, which appear to be either identical or very closely related to the spleen bodies, are also regarded by him as belonging to a new genus, to which he has given the name "helcosoma."

Thirdly, with regard to the flagellate theory, I will not occupy your time by recapitulating the arguments which I put forward in its support. Briefly, in my first communication I suggested that the bodies were possibly degenerated trypanosomata; but this opinion I subsequently qualified in my communications of November 21st, 1903, and February 6th, 1904, to the BRITISH MEDICAL JOURNAL, in which I spoke of them as possible involution forms of trypanosomata, or encysted trypanosomata, and as representing a stage in the life-history of these organisms. My further prolonged study of the atypical forms assumed by trypanosomata has only strengthened my impression that the new bodies represent a stage in the development either of a trypanosoma or of some closely-allied member of the flagellata. I may add that the investigations of Marchand and Ledingham led them to endorse this close resemblance, and also to support the deduction I ventured to base upon it. Some of the forms resulting from the involution of the trypanosomata, as illustrated in the accompanying sketches of actual specimens, are at times

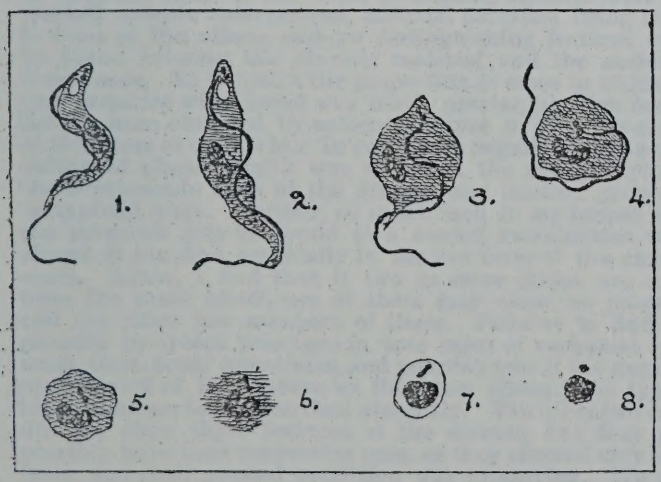


Fig. 1.—Involution forms of trypanosoma brucei. 1, 2, 3, 4, 5, Successive stages in the involution of a trypanosoma; 6, 7, 8, different forms of completely involuted trypanosomata. (Drawn from specimens stained by Romanowsky's method.)

almost indistinguishable from the new bodies, and the resemblance is even more striking in sections of organs stained to display the chromatin of the parasites. The sections, etc., of organs of animals infected with trypanosoma brucei displayed under the microscopes will sufficiently illustrate this resemblance, and I shall pass to the consideration of some recently published work which seems to me to lend further support to the theory of a flagellate origin of the bodies, and at the same time to furnish a possible explanation of their true nature.

In the first place, Schaudinn, in following the various transformations undergone by a blood parasite of the stone owl when taken into the stomach of a mosquito (*Culex pipiens*), comes to the conclusion that this halteridium is in reality a sexual form of a true trypanosome, to which he gives the name trypanosoma noctuae. To give even an outline of this very striking and convincing work of Schaudinn's is impossible in the time at my disposal, so I must limit myself to a few brief references to the points which seem to me to bear upon the present subject. For instance, he describes how at one stage the trypanosomata, free in the mid-gut of the mosquito, lose their typical shape and enter the epithelial cells of the intestine, in and among which they assume a resting form, the body becoming contracted and the flagellum shrinking up into a short rod-shaped structure. In this resting stage division by simple fission may occur, so that frequently large aggregations of these non-flagellated parasites are found in the intestinal epithelium. Further, after describing the mode in which these trypanosomata may push their way between the cells of the muscular coat of the stomach, he says: "When they come to rest here they become almost spherical and the flagellar apparatus reverts to its primitive form," that is, to the blepharoplast or micronucleus from which it was derived. From this resting form a freely mobile trypanosoma is again developed, the flagellar apparatus arising from the blepharoplast by the elaborate mitotic process whose details have been so minutely studied and described by this author.

Again, Prowazek, working on similar lines to those of Schaudinn with a parasite of the house fly—*Herpetomonas muscae domesticae*—finds similar trypanosomal forms which also assume resting forms in much the same manner as trypanosoma noctuae.

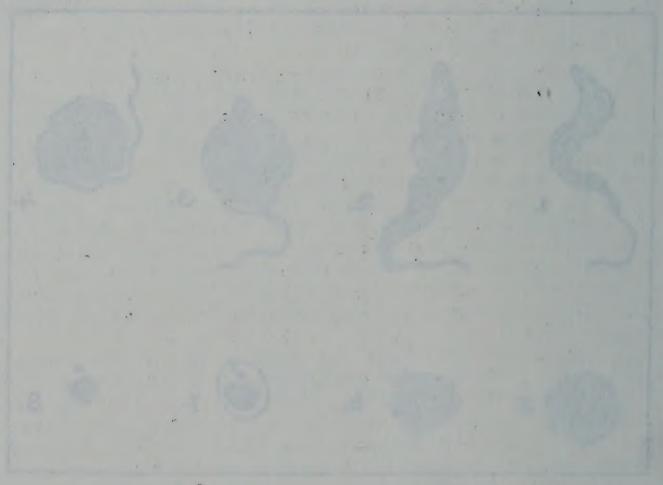
From the descriptions and figures given by Schaudinn and Prowazek of these resting forms of trypanosomata, a very close resemblance may, I think, be traced between them and the new bodies, as we meet with the latter in the mononuclear cells of the liver and spleen, and in this resemblance lies the possible explanation of the flagellate origin of the bodies, of which I spoke just now.

A point in Mr. Christophers' report also strikes me in this connexion as suggestive, and that is the occurrence, in every case that he examined, in the ulcerated intestinal mucosa of what he describes as very large curved micro-organisms, with a single large chromatin mass near the centre, having one end more pointed than the other and somewhat resembling sporozoits. These he regarded as bacteria, but he does not mention whether any attempts were made to cultivate and isolate them, and it appears to me as at least possible from his description that they may represent an intermediate stage between the theoretical intracellular resting form and the free-swimming flagellate.

A fact of great importance in connexion with the possible means by which the parasites are eliminated from the system is the presence of the bodies in the ulcers of the intestinal mucosa. This fact was brought out by Christophers and also by Manson and Low, and, from the frequency with which dysenteric complications have been reported in the course of the disease, it seems probable that this ulceration is a fairly constant feature. The parasites have not yet been found in the urine, but, as their presence in small numbers in the kidney has been noted, this is a possibility not to be overlooked.

With regard to the discovery of Wright, already alluded to, that very similar parasitic bodies are met with in the well-known Delhi boil, it is obviously of the first importance that the identity or non-identity of those parasitic bodies with the splenic bodies should be established, and it is possible that the cercomonads which Ross found in these boils may be developed from, or may develop into, these bodies. Should Wright's parasites prove to be identical with those under discussion, I see no great difficulty in reconciling the marked differences of symptomatology, as bacteriology shows us so many examples of a given germ producing at one time only a local inflammatory process, at another a possibly fatal septicaemia or other grave general affection, the type of disease being determined by such factors as the channel of infection, the virulence of the germ, and the resistance of the host.

Since preparing the above remarks an announcement has been made by Captain Rogers that trypanosomata have developed in cultures of the spleen parasites, and from the details



published by him in the last number of the *Lancet* there would appear to be little doubt that this is actually the case, and that we may soon be justified in taking the connexion between the bodies and trypanosomata as an established fact. If so, it is difficult to overestimate the great importance of this observation of Captain Rogers, which should greatly facilitate the investigation of the many problems which still await solution in connexion with the parasite and the morbid conditions to which it gives rise. Captain Rogers has been good enough to send me a note confirming the announcement made in his telegram, and I am glad to hear that he is making a communication on the subject to this meeting.

II.—LEONARD ROGERS, M.D., M.R.C.P., I.M.S.,
Acting Professor of Pathology, Medical College, Calcutta.

CACHEXIAL FEVER IN INDIA ASSOCIATED WITH CUNNINGHAM-LEISHMAN-DONOVAN BODIES.

IN a recent note[1] I described briefly the parasites found in the spleen in cases of chronic fevers with great enlargement of the spleen in Bengal, and suggested the term "cachexial fever" for the disease as describing its most prominent features, and at the same time retaining the association with the name by which these cases have always hitherto been known, namely, "malarial cachexia." In the present communication, I propose to briefly set forth the results of a study of a number of further cases in the large hospitals of Calcutta. The name of Cunningham is associated with the parasite, in addition to those of the recent discoverers of the organism in the spleens of chronic fevers, for it has been shown by Captain S. P. James, I.M.S., that the bodies described by D. D. Cunningham many years ago in Delhi boil are indistinguishable from those in the splenic cases, an observation which I am able to vouch for, as Captain James kindly showed me his slides from Delhi boil cases, and we were unable to find any differences between them and those in my spleen-puncture slides. Including thirty cases in Dinajpur, I have now performed spleen puncture over sixty times, and that of the liver once, in a case where that organ was much more enlarged than the spleen (Case 6 of the table). Immediately the needle is withdrawn pressure is kept up with a finger over the place for a few minutes, and in no case has even slight perisplenitis occurred, although the coagulability of the blood in many of the cases was reduced.

Frequency of the Disease in Calcutta.

In my previous series of cases in the very malarious district of Dinajpur, I found the new parasites by spleen puncture in only one-third of the cases presenting chronic fever and marked splenic enlargement, malarial parasites being found in some of the others, and no distinguishing features could be found between the chronic malarial and the cachexial fever cases. In Calcutta the proportion of cases in which the new parasites were found was much greater, positive results having been obtained by spleen puncture in over five-sixths of this class of case, while in one of the negative cases a pure culture of plague bacilli was obtained, the patient dying of the septicaemic form of the disease, and another proved to be typhoid fever. Further, as mentioned in my former note, the parasites may be found at a second examination when absent at the first, especially in the low fever of the chronic cases. Again, I find that if two or more slides are made from the same blood, one of them may show no parasites and the other fair numbers of them. Failures to find the parasite by spleen puncture in true cases of cachexial fever must, then, occur sometimes, and possibly two of the negative results were of this nature, as the cases showed the typical blood changes to be described presently. The other two cases did not show these features of the disease, but they may possibly have been recovering ones, as they showed very little fever, and their general condition was improving. We may conclude, then, that the great majority of the cases known hitherto as "malarial cachexia" occurring in Calcutta, at any rate, during the hot-weather months, when true malarial cases are at their minimum, are really cachexial fever due to the new parasites.

The Intensity of the Infection.

Although a single film may be misleading as regards the number of parasites present, still the examination of a series of cases such as that tabulated on p. 647 (Table I)—at least two slides having been made from each case—allows a fairly definite opinion to be formed as to the intensity of the infection in the group as a whole. The number found in each case is indicated in Table I, an examination of which shows that in about half the cases only "a few" were found, which means that they were found only after some minutes' search. In another fourth they were found easily, but not in very large numbers, this degree being indicated by the term "many." In the remaining quarter they were classed as "numerous," meaning that they were very easily found, being occasionally present in nearly every field of the microscope. In many of the cases in which but few were found the patients showed only a low intermittent fever, or none at all, for days together, and were improving and likely to recover. "Many" parasites were, however, found in some such cases, and in one instance this was the case after the temperature had been normal for several days; while in other cases "a few" were found as long as twelve days after the cessation of fever. On the other hand, the parasites were most numerous during marked fever, especially of the double remittent type to be described presently, and in progressive cases in children. When only very scanty in a blood film they could be found in much larger numbers in centrifuged citrated blood, by which means it is possible to find them in such cases much more easily than in smears of spleen blood. In some cases where they were very numerous in the spleen blood several c.cm. of blood was taken from a vein in the arm and centrifuged, but no parasites of any kind were detected in the peripheral blood by this means, so they are probably absent from it. The appearances mentioned in my last note as possibly parasitic in the peripheral blood have not been seen again. Possibly in the rainy season "numerous" parasites may be found in a larger proportion of cases, as I showed some years ago that in the epidemic form of the disease the majority of the cases arose in the rainy season. Still, it will be shown presently that "numerous" parasites were found in a much larger proportion of spleen bloods from kala-azar cases than in those of the endemic disease in Calcutta and Dinajpur, thus confirming my view expressed in 1897 that kala-azar is but an intensified form of what was then known as "malarial cachexia."

Races Attacked.

The great majority of the patients at the Medical College are natives, and my cases include Hindus, Mohammedans, Chinamen, and Burmese women, and also two Europeans. Several of them had first been attacked with the fever while living in Calcutta. In addition to these I have found the parasite in the spleens of four cases in the European General Hospital, two being adults and two children, while several other similar cases clinically are under observation there, so that Europeans not infrequently suffer from the disease. Further, the disease frequently attacks more than one member of a family even among Europeans, a father and child having died of the disease, both with cancrum oris, in the European Hospital recently, while at the present time a mother and son are suffering from the disease there, in both of whom I found the parasite by spleen puncture. This, I pointed out in my original report, was the most characteristic feature of the distribution of kala-azar cases, in which it was the rule rather than the exception in hospital cases for at least half the household to have died of the disease. A similar, although much less marked, tendency is also present in the endemic form.

Clinical Characters.

General.—Time will not permit of detail as to the clinical characters of the disease, nor is it necessary, as "malarial cachexia" is only too well known, while this part of the subject was very fully treated in my book on kala-azar, individual cases of which very closely resemble "malarial cachexia," except in their greater severity and the more rapid course of the epidemic form. When the disease is fully established it is easily recognized by the wasted condition of the patient, contrasting with the tumid belly, due to great enlargement of the spleen, and, to a less degree, of the liver, accompanied by anaemia of variable but usually moderate degree, and, in the later stages, swelling of the feet. Such a case presents no difficulty in diagnosis, except, perhaps, from true chronic malaria, if it really produces such a condition. In this stage, however, but little can be done by treatment, so it is of the utmost importance to try and find means of differentiating the fever in its earlier and more amenable stages. For this purpose I have made a careful study of the temperature curves and of the blood changes in the present series of cases, together with those of former cases of "malarial

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[1] BRITISH MEDICAL JOURNAL, May 28th, 1904. (This paper contains references to other recent work.)

cachexia," which I now recognize to have been cachexial fever. The temperature was taken every four hours, a lesser frequency affording little help.

Temperature Curve.—1. *Chronic Cases.*—In the typical advanced endemic form the temperature curve is extremely irregular, but usually intermittent, running up from 100° to 102° F., and not infrequently remaining normal for days together. Sooner or later, in progressive cases, the temperature rises to a higher level, and a very irregular remittent type appears, the most marked feature of which is a tendency for a double or even a treble rise to take place within twenty-four hours, one rise occurring in the early morning and a second in the afternoon or evening. In this late stage of the disease the hours of the rises are seldom exactly the same on two successive days, while frequently only one rise occurs, especially if the temperature ranges lower than before. As the exacerbation passes away, the intermittent fever with a single daily rise recurs. Chart 1 illustrates such an exacerba-

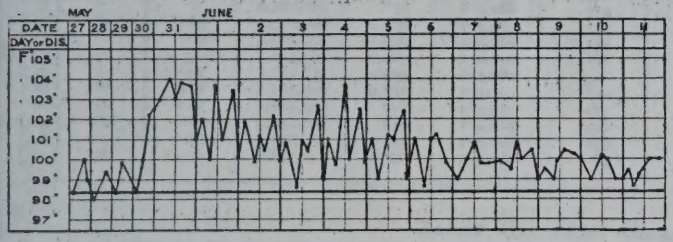

Chart 1.

tion of the fever in a man who had suffered from intermittent fever in hospital for seven months, which became reduced to a stage in which the temperature only rose to 100° occasionally for weeks together by the use of large doses of quinine combined with the hypodermic use of the drug. As long as he took a dose of 10 gr. to 20 gr. by the mouth every morning, he remained practically free from fever, and improved greatly in health; but very soon after the daily dose was reduced to 5 gr. the relapse illustrated in the chart occurred, and the irregular double remittent type of fever appeared.

2. *In Early and Actively Progressive Cases.*—The earliest stages of this fever are still unknown, and it is not until considerable enlargement of the spleen has occurred as a result of long-continued fever that they are recognizable. In Assam I studied cases of fever in infected households, which subsequently went on to become typical kala-azar, but I failed to find any way of differentiating them in the earliest stages from ordinary malarial fever, possibly owing to so many of them being complicated by malaria, as shown by the nearly invariable presence of melanotic pigment in the organs of kala-azar cases after death. Recently I have been able to examine a few comparatively early cases with marked remittent type of fever and progressive wasting, anaemia, and moderate enlargement of the spleen, and in such cases the irregular double remittent type of fever, just described as occurring occasionally in more chronic cases, is much more marked a feature, especially when the temperature runs up to 103° or 104° F. Chart 2 illustrates such a case, two,

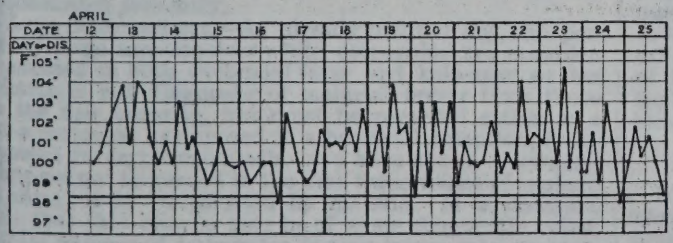

Chart 2.

and even three, rises occurring within twenty-four hours on several days, the new parasites having been found in the spleen blood in considerable numbers. After going on for a month in hospital the temperature became lower and less frequently showed the double rise, thus resembling the chronic forms. Another case which occurred before the new parasites were known showed a regular double rise, at 2 a.m. and 2 p.m., for two weeks, but subsequently became irregular. Further, in a previous paper[2] on tropical fevers I gave a chart with "double daily remissions and highly resistant to quinine," which I diagnosed as malarial remittent on account of a marked increase of the large mononuclear white corpuscles, a change which I shall show presently also occurs in cachexial fever, and this case was probably the early stage of cachexial fever, and it showed the characteristic double and treble remittent curve just described. In the early stages rigors not infrequently occur, and a history of a double daily rise may sometimes be obtained. This characteristic cause, then, appears to be more marked the earlier the case is seen, and if further experience confirms this, it will be an important point in the early diagnosis of the fever—a matter of the greatest practical importance, as it is only in the earlier stages that much good is likely to result from treatment.

The Blood Changes.

In a previous paper[3] on "malarial cachexia" I pointed out that both in the cases hitherto known by that name and in kala-azar there is commonly a marked increase of the proportion of the large mononuclear white corpuscles, and I regarded this as evidence that both forms of the disease were malarial. In my previous note on cachexial fever I recorded the fact that in cases accompanied by the new parasite a similar change was found. In the first-mentioned paper I also pointed out that in "malarial cachexia" the total number of white corpuscles is very greatly reduced, the polynuclears especially suffering, so that there may be less than one-twentieth of the normal number in the blood, and that such cases were very resistant to treatment with quinine, while those cases in which this feature was less marked usually did well under treatment. On going over my old notes and from four temperature charts I find that these cases agree exactly with those in which I have recently found the new parasites, and, as will be seen from a glance at Table I (p. 647), in which are recorded the data of all the cases up to date of tabulation in which blood counts have been made and the parasites also found by spleen puncture.

The Degree of Anaemia.—Bearing in mind that the percentage of haemoglobin in natives of India, and also in most Europeans after some residence, is only from 70 to 80 per cent. of Gowers's standard, it will be observed that the degree of anaemia is usually only a moderate one, while it may be very slight in spite of a marked white corpuscular decrease, as in Cases 15 and 16. The number of red corpuscles also not infrequently reaches over 4,000,000, and is as a rule over 2,500,000, even in advanced cases, while in only a very small number is there a very marked degree of diminution of them.

The Leucocyte Changes.—The number of white corpuscles, on the other hand, shows a most remarkable and constant reduction, the number per c.mm. being less than 2,000 in the great majority of the cases, while it is quite common for them to fall to 1,000 or less. That the white corpuscles are reduced in much greater degree than are the red is evident from the column showing the ratio of the white to the red corpuscles, from which it will be seen that instead of there being 1 white to about 625 red as in a normal subject, the proportion is commonly from 1 to 2,000 to 1 to 4,000, and may be even lower still. Further, on referring to the last column, in which it is noted whether the disease was progressive or the patient was improving and likely to recover, it will be found that all the cases in which the total number of leucocytes was over 2,000 were improving or stationary, with the exception of Case 19, in which a secondary staphylococcus infection and cancrum oris was present, and probably produced a feeble attempt at leucocytosis, resulting in a temporary slight increase above the usual low level of such cases.

When we come to examine the proportion of the different kinds of leucocytes we find that it is the polynuclears which are especially reduced in numbers, while the percentage of the lymphocytes and large mononuclears are relatively increased, although their total numbers per c.mm. are much below the normal. In order to bring out the great reduction in the total number of the polynuclears per c.mm. the numbers have been calculated and are shown in the table. It will be seen that the only cases which showed over 1,000 polynuclears per c.mm. were those which were improving or stationary, having only occasional low fever or none at all. Of the progressive cases, most showed less than 500, or under one-tenth of the normal numbers, while in No. 9 less than one-fiftieth were present, the patient dying the next day of

[2] *Med. Chir. Trans.*, 1903, and *Lancet*, vol. i, 1903.
[3] *Indian Medical Gazette*, November, 1902.

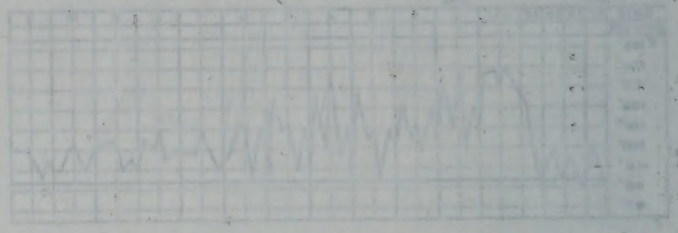

Chart 9.

tion of the fever in a man who had suffered from intermittent fever, implied for seven months, which became subinvolved to a stage in which the temperature only rose to 100° occasionally for a few days, by the use of large doses of quinine combined with the hypodermic use of the drug. As long as he took a dose of 10 gr. to 20 gr. by the mouth every morning, he remained practically free from fever, and improved greatly in health but very soon after the daily dose was reduced to 5 gr. the relapse illustrated in the chart occurred, and the irregular double remittent type of fever appeared.

2. In Early and Actively Progressive Cases.—The earliest stages of this fever are still unknown, and it is not until considerable progression of the spleen has occurred as a result of long continued fever that they are recognisable. In Assam I studied cases of fever in isolated bungalows, which subsequently went on to become typical kala-azar, but I failed to find any evidence differentiating them in the earliest stages from ordinary malarial fever, possibly owing to so many of them being complicated by malaria, as shown by the nearly invariable presence of malarious pigment in the organs of kala-azar cases after death. Recently I have been able to examine a few comparatively early cases with partial remittent type of fever and progressive wasting, enlarged and tender spleen, and the typical type of fever, just described as occurring occasionally in more chronic cases, is much more marked and clearer, especially when the temperature runs up to 104° or 105°. Chart 10 illustrates such a case, thus

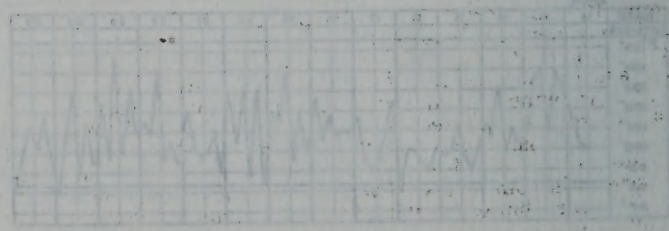

Chart 10.

and every other case coming within twenty days of the commencement of the fever presenting a very long tongue in the fever, but in considerable numbers. After going on for a month in hospital the temperature became lower and less frequently showed the double rise, thus resembling the chronic fever. Another case which occurred below the new parallels were known showed a regular double rise, 24 a.m. and 4 p.m. for the two weeks, but subsequently became irregular

which I was prepared to have been malarial fever. The temperature was taken every four hours, a sample of which is given.

Temperature (Centigrade) Chart.—In this typical case the temperature curve is extremely irregular, but usually intermittent, running up from 100° to 104° or 105° and subsequently remitting normal for days together, sometimes or later in progressive cases, the temperature rises to a higher level, and a very irregular remittent type occurs, the most marked feature of which is a tendency for one, three or even a double rise to take place within twenty-four hours, and the occurrence of the early morning and a second in the afternoon or evening. In this late stage of the disease the rises of the fever are seldom exactly the same on two successive days, while frequently only one rise occurs, especially if the temperature ranges lower than before. As the cachexia progresses, the intermittent fever with a single daily rise returns. Chart 11 illustrates such an case.

Chart 11.

Further, in a previous paper on tropical fever I gave a chart with regards daily variations and highly irregular in quinine, which I diagnosed as malarial remittent, on account of a marked increase of the large mononuclear with mononucleosis, a change which I shall show presently also occurs in cachexial fever, and this case was probably the early stage of cachexial fever, and it showed the characteristic double and triple rise just described. In the early stages rigors are infrequently seen, and a history of a double daily rise may sometimes be obtained. This characteristic cause, then, appears to be more marked the earlier the case is seen, and it further emphasises the fact that it will be an important point in the early diagnosis of kala-azar—a matter of the greatest practical importance—it is only in the earlier stages that much good is likely to result from treatment.

The Blood Changes.

In a previous paper on "malarial cachexia" I pointed out that both in the cases hitherto known by that name and in kala-azar there is commonly a marked increase of the proportion of the large mononuclear white corpuscles, and I regarded this as evidence that both forms of the disease were malarial. In my previous note on cachexial fever I recorded the fact that in cases accompanied by the new parasite a similar change was found. In the first-mentioned paper I also pointed out that in "malarial cachexia" the total number of white corpuscles is very greatly reduced, the polymorphonuclears especially suffering, so that there may be less than one-twelfth of the normal number in the blood, and that such cases were very resistant to treatment with quinine, while those cases in which this lesion was less marked usually did well under treatment. On going over my old notes and from my temperature charts I find that there was a marked exactly with those in which I have recently found new parasites, and as will be seen from a glance at Table I (p. 627), in which are recorded the data of all the examples of cachexial fever in which blood counts have been made and the parasites also found by spleen puncture.

The Degree of Anæmia.—Having in mind that the percentage of haemoglobin in natives of India, and also in most Europeans after some residence, is only from 70 to 80 per cent. of Gowers's standard, it will be observed that the degree of anæmia is usually only a moderate one, while it may be very slight in spite of a marked white corpuscular decrease, as in Cases 17 and 18. The number of red corpuscles also not infrequently reaches over 4,000,000, and is as a rule over 3,500,000, even in advanced cases, while is only a very small number in these a very marked degree of diminution of them.

The Leucocytic Changes.—The number of white corpuscles, on the other hand, shows a most remarkable and constant diminution, the number per c.mm. being less than 3,000 in the great majority of the cases, which is quite common for them to fall to 1,000 or less. That the white corpuscles are reduced to such greater degree than are the red corpuscles, from the column showing the ratio of the white to those of the red corpuscles, from which it will appear that instead of there being a white about 1 to 500 as in a normal subject, the proportion is commonly from 1 to 4,000 to 1 to 6,000, and may be even lower still. Further, on referring to the last column, in which it is noted whether the disease was progressive or the patient was improving and likely to recover, it will be found that all the cases in which the total number of leucocytes was over 4,000 were improving or stationary, with the exception of Case 19, in which a secondary staphylococcus infection and cancrum oris was present, and probably produced a feeble attempt at leucocytosis, resulting in a temporary slight increase above the usual low level of such cases.

When we come to examine the proportion of the different kinds of leucocytes we find that it is the polymorphonuclears which are especially reduced in numbers while the percentage of the lymphocytes and large mononuclears are relatively increased, although their total numbers per c.mm. are much below the normal. In order to bring out the exact relation in the total number of the polymorphs per c.mm. the numbers have been calculated and are shown in the table. It will be seen that the only cases which showed over 1,000 polymorphonuclears per c.mm. were those which were improving or stationary, having only mononuclear low or none at all. Of the progressive cases, most showed less than 500, or under one-tenth of the normal number, while in 8, a less than one-fifteenth were present, the patient dying the next day or

TABLE I.—*Cachexial Fever Cases.*

Sex.	Age.	Haemoglobin.	Haemoglobin Value.	Red Corpuscles.	White Corpuscles.	Ratio of White to Red.	Total Polynuclears.	Polynuclears.	Lymphocytes.	Large Mononuclears.	Parasites.	Remarks.
		Per cent.						Per cent.	Per cent.			
		80	0.80	5,000,000	8,000	1–625	5,600	70	25	5	—	Normal blood of native.
M.	30	40	0.65	3,065,000	750	1–4,087	532	71	24	5	A few	Low fever and dysentery.
M.	35	—	—	5,050,000	1,375	1–3,673	316	23	58	19	A few	Double remittent fever.
M.	46	44	0.54	4,080,000	625	1–6,528	312	51	38	11	A few	Low fever, improving.
M.	—	—	—	4,110,000	1,000	1–4,110	360	36	42	22	Many	Double remittent fever.
M.	50	—	—	4,290,000	625	1–6,864	231	37	46	17	Scanty	Ditto.
M.	56	42	0.70	2,960,000	1,125	1–2,653	798	71	22	7	A few	Died of melaena.
M.	30	45	0.65	3,415,000	1,000	1–3,415	352	35	56	9	A few	Double intermittent fever.
M.	19	46	0.67	3,420,000	2,875	1–1,190	1,811	63	24	12	A few	Low fever, improving.
M.	17	49	0.84	2,920,000	625	1–4,672	103	17	72	11	Numerous	Died of cancrum oris.
M.	40	29	1.23	1,175,000	1,250	1–940	725	58	30	12	A few	Fever and dysentery.
M.	22	44	0.70	3,110,000	2,250	1–1,382	1,386	62	24	14	A few	Improved.
M.	35	54	0.74	3,620,000	2,875	1–1,434	862	30	45	23	Many	Fever stopped, improved.
M.	24	40	0.86	2,330,000	2,500	1–932	1,300	52	32	8	Very few	Ditto.
M.	10	—	—	2,790,000	875	1–3,188	374	43	45	12	Numerous	Fever continued.
M.	37	63	0.69	4,540,000	1,000	1–4,454	456	46	43	11	Many	Cancrum oris, very bad.
M.	21	72	0.69	5,210,000	2,250	1–2,315	1,134	50	38	11	Many	Improving.
M.	32	—	—	1,835,000	1,625	1–1,129	666	41	42	17	Numerous	No change.
M.	10	52	0.77	3,380,000	1,625	1–2,080	341	21	60	18	Numerous	Improved slightly.
M.	16	18	0.77	1,155,000	2,250	1–513	832	37	52	11	Many	Cancrum oris.
M.	21	57	0.87	3,485,000	875	1–3,970	481	55	36	9	Many	Low fever persistent.
M.	20	55	0.67	4,100,000	875	1–4,686	516	59	29	12	A few	Died of pneumonia.
M.	8	45	0.55	4,100,000	750	1–5,466	150	20	59	21	A few	High fever, double remittent.
		56	0.72	3,870,000	1,250	1–3,096	60	5	80	15	—	Five weeks later cancrum oris.

TABLE II.—*Blood Changes in Kala-azar.*

Sex.	Age.	Date Examined.	Haemoglobin.	Haemoglobin Value.	Red Corpuscles.	White Corpuscles.	Ratio of Red to White.	Result.
			Per cent.					
M.	25	8-6-96	30	0.96	1,590,000	750	1–2,210	Died.
M.	18	7-5-96	12	0.50	1,220,000	1,250	1–976	Died.
M.	8	8-5-96	12	0.40	1,500,000	1,500	1–1,000	Died. 80 ankylostoma.
F.	8	15-5-96	45	0.55	4,100,000	7,250	1–781	Early stage.
		9-6-96	—	—	3,130,000	2,500	1–1,212	Died 1-8-96.
M.	30	15-5-96	25	0.61	2,030,000	1,000	1–2,030	Died.
F.	7	23-5-96	16	0.50	1,500,000	750	1–2,920	Died.
M.	22	25-5-96	43	0.79	2,700,000	1,750	1–1,743	Died.
F.	17	16-5-96	28	0.64	2,180,000	2,330	1–948	Very cachectic.
		9-6-96	33	0.69	2,380,000	1,500	1–1,500	Ditto.
		1-7-96	36	0.80	2,250,000	6,500	1–423	Much improved. Eventually recovered completely.
F.	10	17-5-96	72	0.59	6,100,000	6,000	1–1,016	Completely recovered.
M.	36	19-5-96	48	0.65	3,670,000	3,500	1–1,050	Cachectic, but recovered.
F.	40	20-5-96	38	0.51	3,730,000	7,750	1–517	Ditto.
M.	35	22-5-96	31	0.52	3,000,000	2,500	1–1,200	Cachectic.
		2-7-96	43	0.57	3,790,000	9,500	1–389	Improving. Recovered.

ncrum oris. In another case in the General Hospital, ortly before cancrum oris ended the scene, the numbers re reduced to 62, or about one-hundredth of the normal mber; and No. 22 shows a similar extreme reduction. is extraordinary reduction of the polynuclear leucocytes the most remarkable feature of the disease, and of the eatest prognostic importance; while it also affords a ready planation of the frequency with which these cases end, a secondary infection such as cancrum oris, pneumonia, sentery, and phthisis, the patients having so few phagotes that their tissues are unable to resist the invasion of e organisms of these diseases, the frequency of which will demonstrated presently.

The Large Mononuclears.—As already pointed out, the perntage of large mononuclear white corpuscles are considerly increased in both cachexial fever and kala-azar, so that s change is not diagnostic of malarial fevers from those e to the new parasite, but must be regarded rather as a n of a protozoal as opposed to a bacterial infection, being o present in trypanosomiasis, for I have shown elsewhere[4] at they are not increased in the first three weeks of typhoid er, unless it is complicated by malaria. It is, however, sible that this change may be of some diagnostic value, the total number of leucocytes is also taken into account, a study of Table I shows that the increase of the large ononuclears in advanced cases of cachexial fever is only relative one, the total numbers per c.cm. being greatly duced, as are also the lymphocytes. In malaria the ucocytes, as a whole, are also reduced, except in me pernicious cases, but whether uncomplicated malaria oduces the extreme degrees of leucopenia, which I have und so frequently in typical cachexial fever cases, is worthy close investigation, for should it not do so then we shall have in the changes described above a method of differentiating the disease from malaria without resort to spleen puncture. In the early stages, however, no help can be expected from this method, so that the demonstration of a marked large mononuclear increase in cachexial fever necessitates a revision of the opinion I expressed last year[5] that the remittent fevers other than typhoid met with in Calcutta were probably all malarial because they constantly showed the large mononuclear increase, for some may have been early stages of cachexial fever, a point which I am reinvestigating. The fact that nearly all, except a very few showing the double remittent type of fever, readily yielded to treatment by quinine either by the mouth or hypodermically, however, is in favour of the view that they were chiefly malarial. On the other hand, this does not affect my conclusion that all cases of long continued fever, as opposed to remittents, were typhoid, which it was the main object of the paper to demonstrate.

Secondary Infections as the Usual Cause of Death.

I have already referred to the frequency with which secondary diseases bring about the fatal termination of cachexial fever cases, and indicated the extreme reduction in the numbers of the polynuclear white corpuscles as the explanation of this fact. In the cases in Table I some of these complications are illustrated, but for the purposes of obtaining further data I have analysed the *post-mortem* records of all the cases of "malarial cachexia" which I have performed at the Medical College, as the great majority of these cases were certainly really cachexial fever, although mostly also complicated by malaria, as shown by the melanotic pigmentation found in those whose organs were examined microscopically, in 20 of the cases.

[4] *Med. Chir. Trans.*, 1903, and *Lancet*, vol. i, 1903.

[5] *Med. Chir. Trans.*, 1903, and *Lancet*, vol. i, 1903.

TABLE I.—Cachexial Fever Cases.

Remarks.	Parasites.	Large Mono-nuclears.	Lympho-cytes.	Poly-nuclears.	Total Poly-nuclears.	Ratio of White to Red.	White Cor-puscles.	Red Cor-puscles.	Haemo-globin.	Number.
			Per cent.	Per cent.					Per cent.	
Normal blood of native.	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Low fever and dysentery.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Double remittent fever.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Low fever, improving.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Double remittent fever.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ditto.	Scanty	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Died of pneumonia.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Double intermittent fever.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Low fever, improving.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Died of cancrum oris.	Numerous	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Fever and dysentery.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Improved.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Fever stopped, improved.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ditto.	Very few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Fever continued.	Numerous	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cancrum oris, very bad.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Improving.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
No change.	Numerous	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Improved slightly.	Numerous	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cancrum oris.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Low fever persistent.	Many	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Died of pneumonia.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
High fever, double remittent.	A few	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Five weeks later cancrum oris.	—	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE II.—Blood Changes in Kala-azar.

Result.	Ratio of Red to White.	White Corpuscles.	Red Corpuscles.	Haemoglobin Value.	Haemoglobin.	Date Examined.
					Per cent.	

have in the changes described above a method of differentiating the disease from malaria without resort to spleen puncture. In the early stages, however, no help can be expected from this method, so that the demonstration of a marked large mononuclear increase in cachexial fever necessitates a revision of the opinion I expressed last year that the remittent fevers other than typhoid met with in Calcutta were probably all malarial because they constantly showed the large mononuclear increase, for some may have been early stages of cachexial fever, a point which I am investigating. The fact that nearly all, except a very few showing the double remittent type of fever, readily yielded to treatment by quinine either by the mouth or hypodermically, however, is in favour of the view that they were chiefly malarial. On the other hand, this does not affect my conclusion that all cases of long continued fever, as opposed to remittents, were typhoid, which it was the main object of the paper to demonstrate.

Secondary Infections as the Usual Cause of Death.

I have already referred to the frequency with which secondary diseases bring about the fatal termination of cachexial fever cases, and indicated the extreme reduction in the numbers of the polynuclear white corpuscles as the explanation of this fact. In the cases in Table I some of these complications are illustrated, but for the purpose of obtaining further data I have analysed the post-mortem records of all the cases of "malarial cachexia" which I have performed at the Medical College, as the great majority of these cases were certainly really cachexial fever, although mostly also complicated by malaria, as shown by the melanotic pigmentation found in those whose organs were examined microscopically, in 50 of the cases.

¹ Ind. Med. Trans. Cong. and Lancet, vol. i, 1902.

rum oris. In another case in the General Hospital, y before death from this and the disease, the numbers e reduced to 62, or about one-fourteenth of the normal ober; and No. 22 shows a similar extreme reduction. extraordinary reduction of the polynuclear leucocytes he most remarkable feature of the disease, and of the test prognostic importance; while it also affords a ready anation of the frequency with which these cases end, secondary infections, such as cancrum oris, pneumonia, entery, and phthisis, the patients having so few phagocytes their tissues are unable to resist the invasion of organisms of these diseases, the frequency of which will demonstrated presently.

Large Mononuclears.—As already pointed out, the percentage of large mononuclear white corpuscles are considerably increased in both cachexial fever and kala-azar, so that change is not diagnostic of malarial fevers from those the new parasite, but must be regarded rather as a of a protozoal as opposed to a bacterial infection, being present in trypanosomiasis, for I have shown elsewhere they are not increased in the first three weeks of typhoid unless it is complicated by malaria.¹ It is, however, sible that this change may be of some diagnostic value, total number of leucocytes is also taken into account, study of Table I shows that the increase of the large nuclears in advanced cases of cachexial fever is only lative one, the total numbers per c.mm. being greatly ced, as are also the lymphocytes. In malaria the ocytes, as a whole, are also reduced, except in pernicious cases, but whether uncomplicated malaria ces the extreme degree of leucopenia, which I have as frequently in typical cachexial fever cases, is worthy more investigation, for should it not do so then we shall

¹ Ind. Med. Trans. Cong. and Lancet, vol. i, 1902.

Uncomplicated		7
Complicated—		
Cancrum oris and meningitis	1	
Cancrum oris and dysentery	2	
Phthisis	2	
Phthisis and dysentery	1	
Pneumonia	4	
Dysentery	3	
Cirrhosis of the liver	1	
Haematemesis	1	
Cerebral haemorrhage	1	
Total complicated cases		16
Total cases		23

In kala-azar precisely similar complications are met with, only that in more intense forms of the disease deaths from uncomplicated fever are considerably more frequently met with. The cases of death from haemorrhages of various kinds are of interest in connexion with the reduced coagulability of the blood in the advanced stage of the disease, which is easily observed when obtaining blood from a prick of the finger, while, in addition, purpuric haemorrhages in the skin, etc., occur in such cases.

In view of Lieutenant Christophers[6] having found the new parasites in ulcers in the large intestine, the lesions of the bowels are of great importance. In 2 out of his 3 *post-mortem* examinations perforations of ulcers in the large intestine had taken place; but this is a complication I have never met with either in Calcutta or in Assam, so his experience must have been exceptional. On the other hand, dysenteric ulcers in the large intestine were met with in 6 of the 23 cases tabulated above, and scars in 4 more. In 1 case Shiga's bacillus was isolated. In 24 *post-mortem* examinations on kala-azar cases of which I have notes, mostly done by myself, ulceration of the large intestine was only noted in 3, so that it is quite exceptional in that disease. I have elsewhere described a form of pigmented atrophy of the mucous membrane of the small intestine occurring in both the Lower Bengal and the Assam form of the disease, and sections showed much melanotic pigmentation, apparently of malarial origin. These lesions are worthy of examination for the new parasite, material for which, unfortunately, I have not yet obtained, except one case with but few parasites in the spleen, and here I failed to find them in the small or large intestinal walls, although dysenteric ulcers were present in the latter. This case died of gangrene of the lung following pneumonia.

In connexion with the possibility of the infection taking place through the bowel, it is interesting to recall that I showed[7] several years ago that there is a close relationship between a good water supply and a low spleen-rate around Calcutta, and that filtered water supplies had reduced the fever death-rate in the towns of the North-West Provinces, as compared with those without such a supply.[8]

Bacteriological Examinations.

Advantage has been taken of the spleen punctures carried out in the Calcutta hospitals to make cultures from the blood of the spleen in over 30 cases. In a few of the earlier ones contamination with non-pathogenic bacteria occurred, but with improved technique, a long series of purely negative results have been obtained (using both a considerable quantity of broth, to dilute the blood enough to do away with any bactericidal action, agar, and in some of them also coagulated human blood serum), with the exception that in 2 cases of severe cancrum oris pure cultures of staphylococcus pyogenes were obtained, thus proving the secondary invasion of the system by these organisms. In one case a peculiar bacillus grew on a special serum medium only, but it proved non-pathogenic to rabbits and guinea-pigs.

These results confirm my former negative bacteriological results in the case of kala-azar, and finally dispose of Dr. Bentley's Malta-fever theory of the disease.

Further, the absence of the Malta fever coccus in a considerable series of prolonged fevers (one at least of which was contracted in the Punjab, where many cases of Malta fever have been diagnosed on the strength of serum reactions in low dilutions only, including Dr. Bentley's kala-azar cases), raises the question whether most of the so-called Malta fever cases in India may not be cachexial fever, for it is a significant fact that no one has been able to cultivate the micrococcus melitensis from Indian cases. Further, I have been informed by some of those who have obtained serum reactions that they are very rarely, if ever, obtained in high dilutions such as 1 in 80, while Captain Cornwall, working in Madras, has recently[9] shown that reactions with low dilutions can be obtained in healthy persons, and also fairly high ones in cases with no symptoms of Malta fever.

Cultivation of the Protozoal Parasite of Cachexial Fever, and the Development of Trypanosoma from Cunningham-Leishman-Donovan Bodies.

The recent cultivation of trypanosoma has led me to try to obtain similar results with the parasites of cachexial fever by means of adding the blood obtained by spleen puncture to a small quantity of sterile citrate of soda solution, to prevent the blood clotting, and then keeping it under different conditions. Time will not permit me to go into detail with regard to the results so far obtained—which I hope will be published elsewhere very shortly—but I may say that although when the solutions were kept at blood heat the parasites very rapidly degenerated and disappeared, yet when placed in a cold incubator at 27° C. and films made daily, they retained their natural conditions for several days and stained perfectly. Moreover, they increased markedly in numbers, so that in some instances, instead of two or three in a field of an oil immersion lens, as in the freshly-taken blood, after a day or two scores, and even a hundred, very young forms could be found in the same area. Further, very numerous dividing forms were found, even in a single field, although in the original specimens these were very few and far between, and required much searching in specially good specimens to enable even a few to be found, while in my experience the very young forms, which were so numerous in the cultures, are very rarely met with in fresh spleen-puncture blood, and then only within large cells, and not free in a gelatinous zooglea mass as in the cultures. These multiple forms result from the repeated subdivision of the nuclei of the ordinary oval form, as described in my former paper. In addition to this method of division, another frequent manner is a single division of both nuclei, followed by the splitting up of the parasite into two, the separation usually beginning from one end. We have, then, clear evidence of the survival and multiplication of the organism outside the body.

As at a temperature of 27° C. the parasites only lived for three or four days, I next reduced the temperature of the cold incubator to 22° C. This temperature I found to be more suitable to the parasites, as they multiplied more readily, and when very few at first several could easily be found in a field after a day or two. Further, I noticed that many forms of a considerably larger size than I had seen in fresh blood films appeared in a single day. This caused me to look out for flagellated bodies, for on first finding the spleen parasites in Dinajpur I was struck by the resemblance of the double nuclei, one larger than the other, with those of trypanosoma, as Major Leishman had been before. Within the last few days in two of my cultures unmistakable trypanosoma have appeared, together with smaller pear-shaped flagellated bodies like those described by Plimmer in tsetse-fly disease and other intermediate forms. The most marked of these cases (from which the illustrations have been taken) showed completely developed trypanosoma with thick flaggella, macro-nucleus and micro-nucleus after incubation for one day, while the living forms were also seen in the blood culture moving rapidly among the corpuscles. They were quite numerous, and could readily be found after only a short search in a stained film, as will be seen from the specimen sent. This case was a typical one of cachexial fever in a Chinaman, whose spleen blood before incubation showed only fairly numerous oval forms described by Leishman. This case (No. 2 in the table) had also been in hospital for fever two and a half months before, at which time I also found a few typical oval parasites by spleen puncture. The other case in which the trypanosoma have developed was by good fortune a case of kala-azar from Assam, from whom my assistant, Assistant-Surgeon G. C. Chatterjee, kindly got some blood by spleen puncture, and after incubating for five days at 22° C. we found in the citrated blood a number of intermediate forms and a few fully-developed trypanosoma. The fully-formed trypanosoma has, therefore, been already found in my cultures in both the endemic cachexial fever of Lower Bengal and also in the epidemic form of Assam, known as kala-azar, and the true nature of the organism is at least clear, Major Leishman's original hypothesis that the bodies he found were degenerate trypanosoma not being very far from the truth, as they must now be looked on as one stage of the life-history of the new human trypanosoma found by me. In this connexion it is worth recalling that Assistant-Surgeon Chatterjee found a

[6] *Scientific Memoirs Med. Service*, No. 8.
[7] *Journal of the Asiatic Society of Bengal*, vol. lxix, Part II, No. IV, 1900.
[8] *Ind. Med. Gaz.*, October, 1901.
[9] *Ind. Med. Gaz.*, June, 1904.

panosome in the proboscis of a mosquito caught near Calcutta as long ago as October, 1901 (*Indian Medical Gazette*), while I also desire to acknowledge his help in making microscopical examinations of my cultures.

Prophylaxis and Treatment.

It is usually stated that quinine is quite useless in this form of fever, and this is certainly frequently so in advanced cases with but a very small number of polynuclear white corpuscles remaining. I am, however, unable to agree with the opinion that the drug is always useless in this fever. In the first place[10] Dr. Dodds Price has absolutely proved that the drug is a reliable prophylactic against the most virulent form of the disease, namely, kala-azar. I have also frequently seen the fever stopped or greatly decreased by quinine in cases in which over 2,000 leucocytes were still present in the blood, while in chronic cases on leaving off the drug the fever often rises to a considerably greater height than while it was being taken regularly. Further, once the fever has been reduced a single large dose daily will often prevent a relapse. Dr. Dodds Price, as a result of his unrivalled experience of the epidemic form of the disease in Assam, recently wrote to me on this point as follows: "Nothing will induce me at present to admit that quinine is useless. I know, and so do you, that it often fails, but the same can be said of any drug, including mercury in syphilis, while as a prophylactic no sane person can deny its utility." I feel convinced that when we can diagnose cachexial fever in a comparatively early stage—that is, before nine-tenths or more of the polynuclear corpuscles have been destroyed—then we shall get better results by the use of quinine, although it may have to be given hypodermically, or, perhaps, even intravenously.

The only other method of treatment I have time to refer to is one which I recommended in kala-azar seven years ago, namely, the use of red medulla tabloids, or fresh uncooked bone marrow. I was led to try this by finding the yellow marrow in the shafts of the long bones invariably converted into red marrow in fatal cases of the disease, and I looked on this as an effort on the part of the system to repair the damage to the blood caused by the prolonged fever. As, according to Ehrlich, the polynuclear white corpuscles are mainly formed in the red marrow, they, as well as the red corpuscles, may be expected to be increased by this treatment. I have recently been watching the effect of this method on the blood in several cases in which the new parasites were found in the spleen, and in two cases in which only the intermittent type of fever was present the leucocytes were nearly doubled in a few weeks and the general condition improved, although the degree of fever remained unchanged. In another case in which the remittent type of fever continued there was some increase in the total leucocytes, but the differential count showed a continued decline in the polynuclears, cancrum oris set in, and the case terminated fatally (No. 22). It is not to be expected that this treatment will have a direct effect on the fever, but if this can be controlled or is mild or absent for a time, then a more rapid renewal of the leucocytes may be brought about, and the resisting power of the patient against the fatal secondary infections already mentioned may be increased, and recovery eventually occur.

Epidemic Cachexial Fever or Kala-azar.

In my report on kala-azar I laid great stress on the fact that, individually considered, cases of this disease were quite indistinguishable from "malarial cachexia," although when groups of cases were noted it was found to be more virulent and to spread through households, villages, and districts in an epidemic manner. It was this very close resemblance to malarial cachexia, and the frequent presence of malarial parasites at times in all stages of different cases, although they were often absent for long periods in individual cases, that led me to think that the disease was entirely malarial in its origin. The recent discoveries of the new parasites in "malarial cachexia" cases naturally lead to the possibility of their presence in kala-azar being raised, and on my return to India, as soon as I had confirmed the presence of the new parasites in "malarial cachexia" cases in Lower Bengal, I obtained some slides of spleen blood from kala-azar cases, thanks to the very great kindness of my old friend, Dr. Dodds Price, and, as already reported, I found the parasites in five out of six cases, the remaining negative case being one which was reported to be improving and likely to recover. These observations were made before the recent announcement by Dr. Bentley[11] that he has abandoned his Malta-fever theory of the disease in favour of the new parasites. Since my last note was written, Dr. Price has very kindly sent me three further series of spleen bloods taken by puncture during life in typical kala-azar cases, together with notes and charts of the cases, so that I have now been able to examine 17 more cases, making 23 in all. They included cases of from three months to three years' duration, half of them being from five to eight months, and nearly all presented persistent fever. Of the 17 new cases, the new parasites were found in 16, although in 2 of them were only found in the second slide examined. Not only were the parasites nearly constantly found, but in a considerable majority of the cases they were present in extremely large numbers, being present in nearly every field of the microscope, and often several in a field. Such numbers were only found in quite a small proportion of the endemic cases examined in the Calcutta hospitals and in the Dinajpur district, so that I am convinced that the parasites are present in larger numbers on the average in the epidemic form of the disease in Assam than they are in the endemic form in Lower Bengal, this being in accordance with the suggestion of Major Ross that the epidemic nature of the former was due to "numerosity" of the parasites, although he was writing of the malarial parasites, having agreed with my opinion, after a short investigation of the disease in Assam, that kala-azar was malarial in nature. It is further worthy of note that most of the cases in which I found comparatively few parasites were noted by Dr. Price to be favourable cases in which he considered the prognosis to be fair or even good, while the cases in which he gave a bad prognosis nearly all showed very numerous parasites. As he has had over ten years' daily experience of large numbers of cases, his prognoses may be accepted as reliable, several of them having been already confirmed, and we may conclude that there is a relationship between the number of parasites and the severity of the disease, as is also the case with the endemic form in Bengal. It appears, then, to be highly probable that kala-azar owes its peculiar features of persistent fever and rapid cachexia to the new parasite, although its very frequent complication with malaria is evidenced by both the common presence of the malarial parasites, especially in the malarial rainy fever season when most of my examinations were made, and by the constant or nearly constant presence of fine melanotic pigment throughout the spleen and liver, etc., after death.

The Blood Changes in Kala-azar.—In my original report I dealt very fully, in a special section, with the blood changes in kala azar; but as my notes were fortunately saved from a fire in which all my microscopical slides were destroyed, it will be worth while to compare the results then obtained with those of endemic cachexial fever with the new parasites given in an earlier section of this paper. The differential leucocyte count was not done, but the total red and white corpuscles were counted in upwards of 50 cases, and repeatedly in many of them, including a few very early cases, and also cases whose recovery from an advanced condition was watched. The tabulation of a few cases will illustrate the changes best. The first seven shown in Table II (p. 647) are a consecutive series of progressive ones, while the last five are consecutive cases, which, although showing a markedly cachexial condition, were improving, and eventually recovered. No. 4 shows a loss of nearly two-thirds of the white corpuscles within less than a month, while the rest of the seven progressive and fatal cases show less than 2,000 leucocytes. Of the cases which recovered, No. 8 was the most remarkable, for the girl was extremely wasted, while her spleen reached nearly to the level of the anterior superior spine, and diarrhoea had set in. After the failure of iron and arsenic and other treatment to effect any improvement, I put her on red medulla tabloids, and in less than a month the leucocytes had increased from 1,500 to 6,500, while her general condition had improved to a most remarkable extent, and she eventually completely recovered, became quite plump, left the hospital, and was married shortly afterwards. The other cases all had over 2,000 leucocytes when examined, and all made good recoveries, Case 12 showing a very marked increase of the leucocytes to nearly four times their former number within six weeks, accompanied by an equally marked improvement in his general condition.

It is clear, then, that the blood changes in the two forms of the disease are identical; for I showed in my paper on "malarial cachexia" that the differential leucocyte count in kala-azar is just the same as in the endemic cases, and have

[10] *Indian Medical Gazette*, October, 1902.

[11] *Journal of Pathology and Bacteriology*, 1903.

recently confirmed this observation in slides sent by Dr. Dodds Price from cases showing the new parasites, and thus go far to support the conclusion derived from finding the parasites in every progressive case of both forms of the disease, that endemic cachexial fever of Lower Bengal is similar in its pathology to the epidemic form known as kala-azar, as I originally maintained in my report on the latter disease in 1897.

Segregation as a Means of Eradicating Kala-azar.

The remarks already made on the treatment of cachexial fever apply equally well to kala-azar, the greater intensity of the latter being borne in mind. It only remains to refer to the latest evidence concerning the value of the methods I advised in 1897 for the eradication of the disease from infected tea-garden coolie lines, the success of which I have already reported elsewhere.[12] Where a line was badly infected all the healthy coolies in whose households no cases of the disease had occurred were removed to a new site at a distance of half a mile or more from the old one, and all newly-imported coolies also put in the new lines. The following extract from a letter I recently received from Dr. Dodds Price on the subject gives an admirable account of the results of these measures. He writes: "I wonder if you are puzzled that I should always be able to get cases when I have so plainly stated that the disease can be stamped out of tea estates if proper precautions are taken. If you are, the answer goes still further to prove the correctness of my opinion. Kala-azar is only existent in gardens where in addition to building new lines the precaution of destroying the old houses and sites, and taking care to allow none but non-infected coolies into the new lines, has not been properly carried out. Here at Amluckie kala-azar got very bad; new lines were built and remain healthy, but the older time-expired coolies refused to turn out of the old lines, and over 60 per cent. of them are now dead of kala-azar! At Rangamati and Nonoi we still have cases for the same reason, but at Old Solonah, where the disease accounted for hundreds, we never see a case, and even remittent fever hardly ever occurs. Here the most stringent measures were taken, and after a death-rate of over 10 per cent. up to 20 per cent. for several years, we only lost 9 souls last year out of a population of 500, and this year to date (June 2nd, 1904) we have had only 2 deaths."

It is unnecessary to add anything to this plain statement of facts to prove the complete success of the segregation measures which I advised for eradicating kala-azar from infected coolie lines, for the Old Solonah lines were the ones where these measures were first undertaken, and the new lines still remain free after over seven years, although nearly 100 healthy people from the infected lines were moved into them. I should, however, state that Dr. Price had in one garden arranged for a large batch of new coolies to be put in separate new lines, instead of in old infected ones, at a still earlier date with marked success, and it was this example, as well as the action of some villagers in deserting their old houses, and the proof which I gave of the communicability of the disease, which led me to advise the bolder measure of moving out all the healthy coolies from the already badly-infected lines during the cold weather months, when I found infection to be at a minimum and fresh cases rarely occurred. The success of this measure, which Dr. Dodds Price deserves great credit for first carrying out so thoroughly, also demonstrates the local nature of the infection, and points to the soil or water as the habitat of the parasite outside the body, or some form of animal life with such a location.

In conclusion, I desire to acknowledge my great indebtedness to Dr. Dodds Price for sending me kala-azar spleen films, and to Lieutenant-Colonel G. A. F. Harris, I.M.S., and Major F. P. Drury, I.M.S., Physicians to the Medical College Hospital, for allowing me to make use of their cases. The first successful cultivation of the trypanosoma was from a patient of Lieutenant-Colonel Harris.

[12] BRITISH MEDICAL JOURNAL, September 24th, 1898.

Under $\frac{1}{12}$ oil immersion lens and ocular 204.

Description of Figures.

Series I. Showing division of a Leishman body into two, as seen in freshly-drawn blood from the spleen of a kala-azar case.

Series II. Showing method of division, plasmodial stage, into a number of small ones in a culture in citrated blood. These forms also occur in the spleen during life, but appear in very large numbers in cultures.

Series III. Showing the development of trypanosoma from the plasmodial form (Cunningham-Leishman-Donovan bodies).

1. Oval body becoming pear-shaped, the micronucleus passing towards the thin end, from which a thin flagellum is seen arising.
2. Bodies elongated with separation of the micronucleus and macronucleus, but without definite flagella.
3. Body much enlarged with large macronuclei, which are assuming the appearance found in the amoeboid forms (No. 6), while on division it will resemble No. 4.
4. Form intermediate between Nos. 3 and 7.
5. Small flagellated form intermediate between the plasmodial form and the amoeboid form (No. 6).
6. Large oval flagellated forms with large granular macronucleus and flagellum arising from the micronucleus, exactly similar to the amoeboid stage of T. brucei described by Rose Bradford and Plimmer. Nos. 2 and 6 were found in a single field.
7. Double elongated flagellated form beginning to resemble a trypanosoma.
8. More advanced double form.
9. Single form with shape of a trypanosoma and well-marked macronucleus and micronucleus and flagellum.
10. Similar but larger form like a full-grown trypanosoma, except that the undulating membrane has not yet developed and the micronucleus is still at the anterior end, as in the amoeboid stage of the organism. A complete membrane has not yet been seen, the organisms having died out after reaching this stage. The very close resemblance of the above forms to those described by Rose Bradford and Plimmer, after a prolonged study of the disease in many animals, can leave no doubt as to the present organism being a trypanosoma, especially when it is stated that all of this series except No. 3 were found in a single film from a one-day culture of the plasmodial form (Leishman bodies) found in the spleen in cases of cachexial fever.

Under $\frac{1}{12}$ oil immersion lens and ocular 204.

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HUMAN PIROPLASMOSIS.

UNDER the above heading I am contributing a short paper to the Association's meeting. I have limited myself to the clinical side of the question, as abler hands than mine will doubtless have more to say on the nature of the parasite itself. I have for the present accepted Laveran and Mesnil's determination of the organism in the genus Piroplasma. Leishman first found the parasite in November, 1900, in smears of spleen pulp taken *post mortem;* independently of him I met with the parasite in the same organ, also *post mortem*, on April 9th, 1903. On June 17th, 1903, I procured the parasites in blood taken by puncture from the spleen during life. Besides the spleen, the parasites are also found in the peripheral circulation when the temperature is above 103° F. (this find of mine has been confirmed by Laveran and Mesnil); in the liver, bone marrow, submucosa of the large intestines, ulcers of the skin, and ulcerations of the mouth; occasionally in the blood from the kidneys and suprarenals.

I have had up to the date of writing this paper, June 16th, 1904 (exactly a year since I first found the parasites in the spleen blood during life), 72 cases in my wards only. The total admission for the same period was 1,304, giving a percentage of 5.52 for natives and Eurasians collectively; to take them separately, the percentage amongst natives was 6.79, and Eurasians 2.38. In my wards no cases were found amongst Europeans, but a few were admitted in the wards of the other physicians, where the disease is of as common occurrence. The disease attacks the poorer class of natives of both sexes and all castes and creeds, Eurasians and Europeans less frequently. Age is no bar to infection. In Madras the disease is chiefly endemic in the insanitary native quarter of the city called Blacktown. A few have sought admission from a village twenty miles north of Madras, one from Rangoon (?), one from Hyderabad, and another from Bassein, Burmah.

The most characteristic feature of this disease is an enlarged spleen, irregular pyrexia unaffected by quinine, and the absence of the malarial haematozoa in the peripheral circulation.

To go more into details, I give the results obtained from observation of the 72 cases admitted into my wards during the last twelve months. The temperature is of an irregular type with occasional lapses of apyrexia. In the beginning it is of a marked intermittent type, varying from 97° to 103° or 104° F., of daily occurrence, coming on chiefly in the afternoon, associated with shivering; in the later stages it simulates hectic with profuse night sweats. In a few cases the intermittent temperature occurs twice daily; when any complication is present, as broncho-pneumonia or cancrum oris, the pyrexia is continuous or subcontinuous. The four temperature charts (attached) will show the various forms of the pyrexia. The spleen is enlarged in nearly all the cases; in five only was there no enlargement of this viscus. The increase is, as a rule, not great, the organ usually extending down to the level of the umbilicus; rarely, however, has the pelvis been reached. The size of the spleen varies according to the temperature; in some instances, the variation in size has been marvellous, with fever the spleen has been below the umbilicus, and in a week or ten days, on the onset of apyrexia, the organ has contracted and disappeared underneath the ribs, but for a time only; with the reappearance of pyrexia the spleen has as quickly increased in size, and within a few days attained its former enlarged proportions.

The liver is not so invariably affected in size, and it was only in 27 cases that an increase in bulk was noticed, usually to the extent of 1 in. to 2 in. below the costal arch.

Diarrhoea was present in more than half the cases (40 out of 70), the motions were of a dysenteric character, with slime and blood; this intestinal symptom was not always present, but recurred with the severity of the disease. Occasionally ankylostomata, rhabdonemata and balantidia were found in the stools, but their presence was by no means a constant feature of this ailment. Intestinal ulcerations were present, chiefly in the large intestines; their perforation gave rise to peritonitis and death in some cases.

In nearly all the cases there were skin eruptions. The skin was dry, furfuraceous, and irritable. Sometimes there were eruptions simulating those caused by the itch mite; by the scratching of these small ulcers were formed; in two cases such ulcers reached the size of a rupee, and had a great resemblance to Delhi boil.

Subcutaneous haemorrhages or petechiae were present in 12 cases, especially over the chest and ankles, outcrops of these appeared and disappeared, and were a prognosis of bad augury. Pigmentation of the skin was very prevalent noticeable usually on the palms of the hands and the soles of the feet; in a few cases in the buccal mucous membrane, tongue and bulbar conjunctivae. A general pigmentation of the whole body is better marked in light complexioned Eurasians. In native patients who are not carefully tended or washed the dry, furfuraceous skin remains on and becomes in time dirty and black-looking. This is most probably the darkening or blackness of the skin spoken of in connexion with kala-azar. In a few of my Eurasian cases the whole of the skin took on an icteric tinge a day or two previous to death.

Cancrum oris, inflammation and ulceration of the gums and hard palate, very occasionally suppurative tonsilitis, were present in 22 cases.

Associated with these affections of the mouth and pharynx were 4 cases of suppuration of the middle ear. Another constant feature is oedema of the feet, occurring in more than half the cases.

As to the lungs, bronchitis was very prevalent; half the number were thus affected. About six patients suffered from pleurisy with serous effusion, and one had haemothorax; broncho-pneumonia occurred in two. Rarely was ascites found to be present; in one patient there was a considerable amount of blood in the peritoneal cavity; this was detected before splenic puncture, and therefore was not due to that operation.

As to the mortality, 22 died, 7 were removed moribund, and with the exception of 3 still in hospital, the remainder were discharged at their own request, invariably in a much worse condition than on admission; indeed, few of these had any prospect of surviving more than a month or two. In only one case, that is No. 65, whose case and temperature chart is attached, was there any semblance to a cure.

The causes of death were—6 from general infection, 1 from cancrum oris, 1 from oedema of the glottis, 6 from diarrhoea 5 from peritonitis, 1 from broncho-pneumonia, 1 from tubercle of the lungs, and 1 from haemorrhage after splenic puncture.

The blood examinations in cases of piroplasma infection always show a marked decrease of the red blood corpuscles; these vary from 2,000,000 to 3,000,000 to the cubic millimetre. There is no actual increase of the leucocytes, but a relative one of the mononuclears, as in malaria. The average differential leucocyte count in ten cases gave the following result: Polymorphonuclears, 62.56 per cent.; mononuclears, 21.58 per cent.; transition, 2.04 per cent.; lymphocytes, 9.22 per cent.; and eosinophiles, 4.60 per cent.; the number of mononuclears varying from 6 per cent. to 46 per cent.

The urine usually contains albumen and invariably pigment. The faeces, as mentioned before, contain in a few of the cases balantidia, ankylostomata, and rhabdonemata. Quinine has been given by mouth, hypodermically, and intramuscularly *ad nauseam*, with no appreciable result. The same may be said of other less suitable drugs—that is, arsenic, salicylate of sodium, carbolic acid, creosote, tincture of iodine, etc.

The *post-mortem* find is generally an enlarged, pigmented, or unpigmented spleen; liver enlarged, congested, or cirrhosed; at times there is pigmentation present; intestines, especially the large, deeply congested, inflamed, or ulcerated.

Owing to limit of time I can only give a short history of four cases with their temperature charts:

1. CASE NO. VIII.—Vedachellan, a healthy looking and well-built boy, aged 12 years, lives at Perambur; fever one and a half month's duration. Spleen enlarged to umbilicus, liver normal, no diarrhoea and no oedema of the feet. During his stay in hospital for over two months had irregular pyrexia and had become a little thinner when discharged.

2. CASE NO. XXIV.—Narainsami, an emaciated, very dark complexioned man, aged 35 years, lived at Blacktown; history of fever of two months' duration with dysenteric motions. Was three months in hospital suffering from typical pyrexia, dysenteric motions, cough, oedema of feet and soreness of mouth. The strange feature about this case was that the spleen and liver were not enlarged, and it was with some difficulty that the spleen could be punctured. He died, and a necropsy was held by me. The following especial features were noted: Fourteen ounces of blood-stained fluid in the abdominal cavity; parietal peritoneum, especially in the pelvis and sides, mesentery and omentum, covered with numerous petechial spots of recent origin, some, however, appear old, like miliary tubercles. Intestines—lower part of the large—inflamed and ulcerated. Spleen normal, of a brownish-pink colour, non-pigmented. Liver very slightly enlarged, congested, non-pigmented. Suprarenals enlarged. The other viscera call for no mention.

3. CASE NO. XLVI.—Sivaraman, a delicate native boy, aged 13, lives in

[illegible] Donovan, I.M.S.

[illegible] Hospital, Madras.

[illegible] KALA-AZAR.

[illegible] a short paper in Association [illegible]. I have limited my call to the side of the question, as other hands than mine will [illegible] more to say on the nature of the parasite [illegible] I have for the present accepted Leishman and Donovan's [illegible] organism in the spleen. Prospects [illegible] found the parasite in November, 1903. In [illegible] of [illegible] past months; frequent [illegible] permitted in the same organ, also [illegible] 1904. On June 7th, I presented [illegible] blood taken by venipuncture during the spleen [illegible]. Besides the spleen, the parasites are also found [illegible] the temperature is above [illegible] of acids has been confirmed by Lavران [illegible] the liver, bone marrow, submucosa of the [illegible] intestine, ulcers of the skin, and ulcerations of the [illegible] in the blood from the gingivæ and [illegible].

I have had up to the date of writing this paper, June 15th, [illegible] a year since I first found the parasites in the [illegible] blood during life, as stated in my work [illegible]. The [illegible] for the same period was 1.59, giving a percentage of 5.24 for natives and Europeans collectively; to [illegible] separately, the percentage among natives was [illegible] and Europeans 2.5. In my work in cases were found [illegible] Europeans, but a few were admitted in the wards of the [illegible], where the disease is of an common occurrence. The disease attacks the poorer class of natives of [illegible] and creeds, Europeans and Euro-[illegible] are frequently [illegible] to infection. In Madras [illegible] in the insanitary parts of the city called Bunderows. A few have sought [illegible] from a village twenty miles north of Madras, one [illegible] from Kurnool (?), one from Ongole, and another from [illegible], Burma.

The most characteristic feature of this disease is an enlarged spleen, irregular pyrexia manifested by quinine and the absence of the malarial parasites in the peripheral circulation.

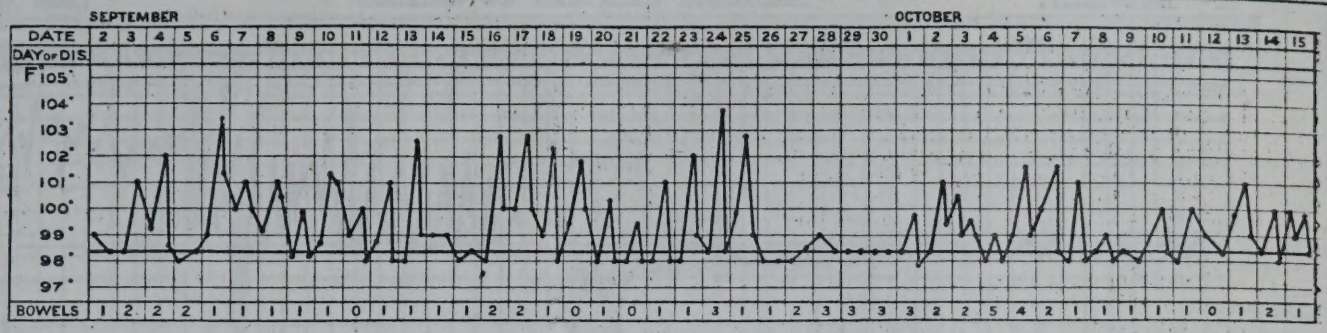
To go more into detail, I give the results obtained from observations of 1904, as compared with my work during the last twelve months. The temperature is of an irregular type with occasional lapses of apyrexia. In the beginning it is of a marked intermittent type, varying from 97° to 105° F. Of late it has become more on quinine, mostly on quinine in the after-noon, associated with shivering; in the later stages it simulates hectic with profuse night sweats. In a few cases the intermittent temperature occurs twice daily; when any complication is present, as bronchopneumonia or pneumonia, the pyrexia is continuous or sub-continuous. The temperature chart (attached) will show the various forms of the pyrexia. The spleen is enlarged in nearly all the cases; in five only was there no enlargement of this viscus. The increase is, as a rule, not great, the organ usually extending to the level of the umbilicus; rarely, however, has the spleen been [illegible]. The size of the spleen varies according to the temperature; in some instances, the variation in size can be noted in a few days, with fever the spleen has been below the umbilicus, and in a week or ten days on the onset of apyrexia, the organ has contracted and disappeared under the costal margin, but in a time only; with the temperature the spleen has gradually increased in size, and within a few days attained its former enlarged proportions.

The liver is not so invariably affected in size, and I was only by no means that an increase in bulk was noted, usually to the extent of 1 in. below the costal arch.

Diarrhœa was present in more than half the cases (so out of 70 the motions were of a dysenteric character, with slime and blood). This intestinal symptom was not always present, but invariably with the severity of the disease. Irregularly anæmic, rheumatic and [illegible] were found in the cases, but [illegible] was by no means a constant feature in this affection. Intestinal disorders were prominent, [illegible] in this large institution; their performance gave rise to peritonitis and death in some cases.

In nearly all the cases there were skin eruptions; the skin was dry, [illegible], and [illegible]. Sensations were [illegible] by the tick mite; by the [illegible] of these small ulcers formed; in two cases [illegible] the skin of a rupee, and had a great [illegible]

[illegible]



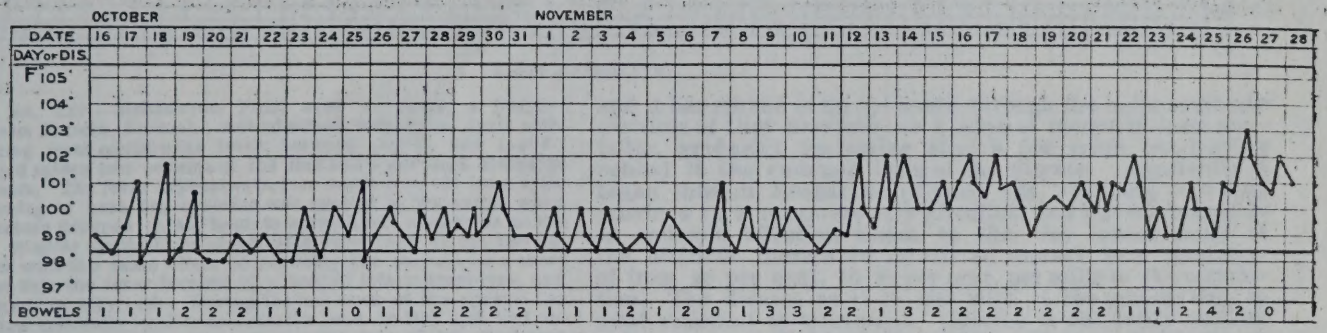
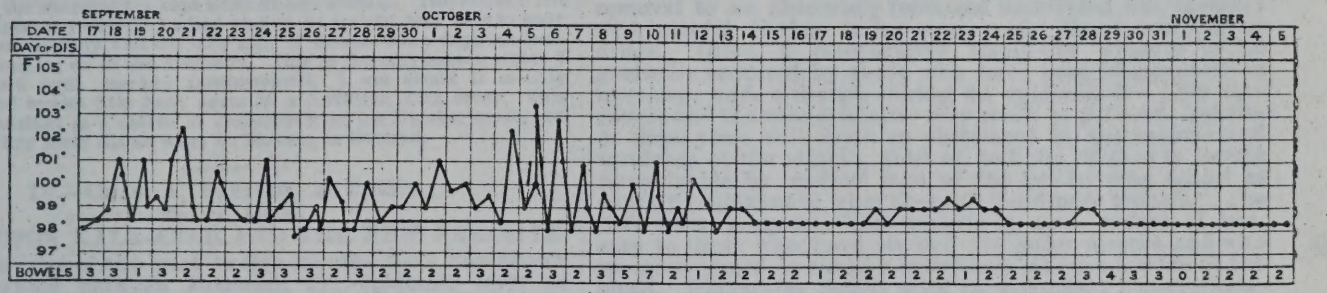


Chart 1.—Case VIII.



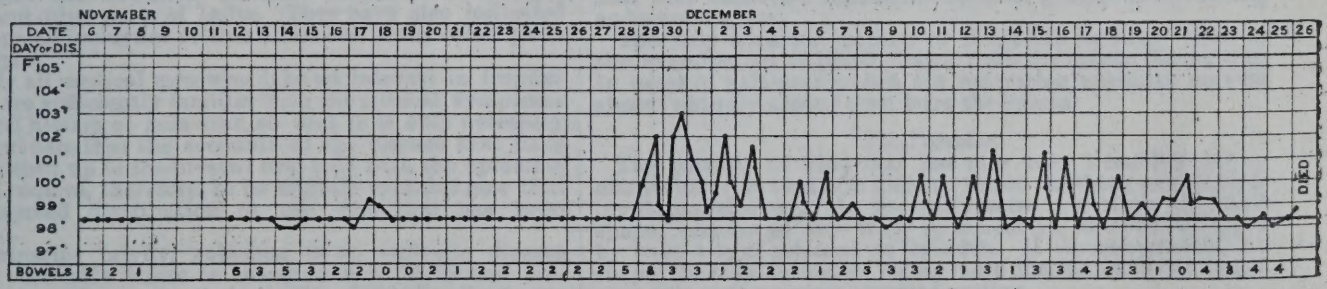


Chart 2.—Case XXIV.

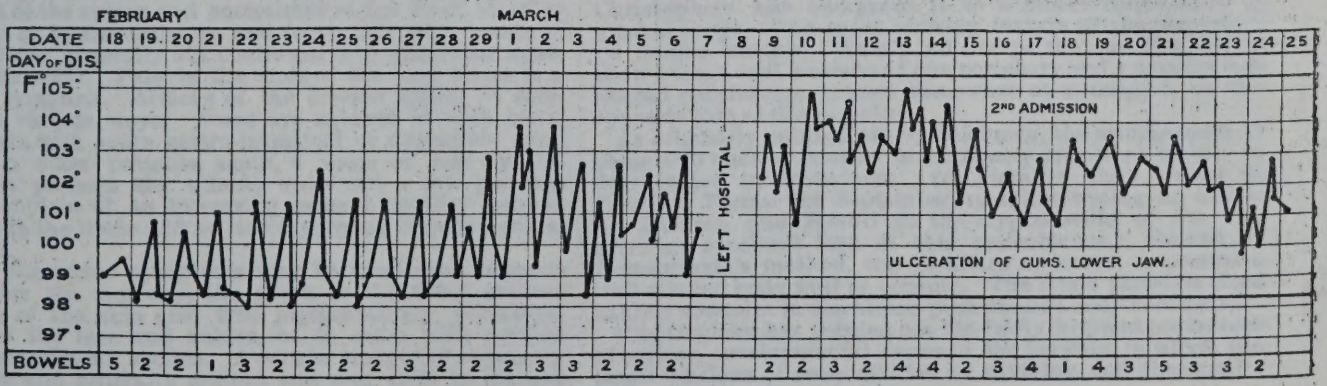


Chart 3.—Case XLVI.

Blacktown; spleen enlarged to umbilicus, liver normal. Has had fever for six months, the splenic enlargement noticed two months ago, occasional oedema of feet, with diarrhoea and cough. Was a little over a month in hospital. During the latter part of his stay he suffered from ulceration of the gums over the left incisors. He left at his own request much weaker than on admission.

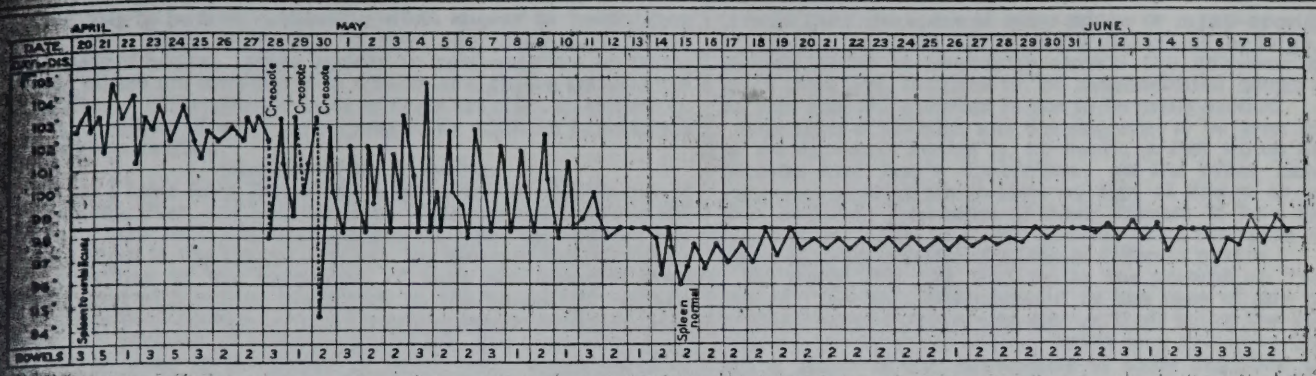


Chart 4.—Case LXV.

CASE NO. LXV.—Mahadevan Nair, aged 21 years, a hospital assistant from Bassein, Burmah; was admitted very ill on April 20th, 1904, suffering from continuous fever, between 103° F. and 104° F., with enlarged spleen and oedema of the feet and a purulent discharge from both ears. The fever kept more or less continuous till June 27th. On the morning of next day creosote was applied to the axilla, when the temperature dropped in an hour to normal, but rose again in the afternoon. Similar applications of creosote were made on the two following days, with the same effect of reducing the pyrexia for a short time. After this the fever became of a marked intermittent type, and reached normal on May 12th. During the last week of the pyrexia the spleen became gradually smaller and smaller, and on May 15th had regained its normal size. From May 12th to the date of his discharge (June 9th) the temperature kept more or less normal. The patient left hospital apparently cured; he had picked up weight, was able to walk about and eat heartily, and the only sign of disease was a slight oedema of his feet coming on in the evenings. This is the only case in which I have noticed such marked improvement. I am afraid it is only illusory, and expect him back again in a fortnight with fever. This hospital assistant is a native of Tellicherry, on the Malabar coast, and had never any fever till he went to Bassein in Burmah.

IV.—CHAS. A. BENTLEY, M.B.Edin.,

Tezpur, Assam.

NOTES UPON KALA-AZAR AND THE NEW PARASITE.

THE discoveries of the past twelve months have now shown the connexion between kala-azar, the epidemic fever of Assam, and the so-called malarial cachexias of Bengal, Madras, and other parts of India. They have also indicated the widespread incidence of this disease in many other parts of the tropics.

Probably all medical men who take an interest in tropical medicine are sufficiently familiar with the clinical symptoms and general history of kala-azar, so that it is only necessary to point out here that the accounts of the disease that have been published up to the present deal only with the epidemic form, and require, therefore, to be slightly modified now that the widespread distribution of the condition has been recognized.

To summarize briefly, kala-azar is an endemic disease occurring over wide tracts in many parts of India and probably in many other parts of the world. Occasionally it may appear in epidemic form. It is characterized by gradual enlargement of the spleen and sometimes of the liver, together with more or less emaciation and frequently with bursts of irregular fever, generally of a continued or a quotidian intermittent character. Pain in the ends of the long bones is a frequent symptom. Attacks of the disease appear to commence in various ways. Some are ushered in with fever, others begin with acute gastro-intestinal or dysenteric symptoms. In other patients, again, a more or less typical pneumonia prefaces the attack, while not a few patients merely complain of an increasing general debility coupled with pain in the limbs and an accompanying enlargement of the spleen.

Among the minor symptoms may be mentioned haemorrhages from the stomach, the gums, or the nose; gradual darkening of the skin (not true pigmentation); occasional oedema of the face and ankles, or, in cases with marked hepatic enlargement, ascites. A certain amount of secondary anaemia is also generally present and may exist in marked degree.

The disease attacks people of every age and both sexes. Attacks may last for several years or run through a rapid course of a few months. The dysenteric form is usually rapidly fatal.

The disease occurs sporadically over the whole of Assam, and it has spread as an epidemic through the more southerly districts of that province, as a wave of increased fever mortality, gradually decreasing after a few years, but leaving behind it the endemic form of the disease. Apparently it began thus in Bengal many years ago, sweeping over that province in a north-easterly direction, and leaving behind it an endemic affection which to this day causes many of the districts therein to return an annual fever mortality of from 20 per cent. to 75 per cent. per mille of the population. The disease as it is met with at the present time is most resistant to treatment. Quinine is absolutely useless either as a prophylactic or specific. Change of climate or removal to an absolutely fresh and uninfected site, together with careful dieting, is far more useful than treatment by drugs. Often a comparative immunity appears to be gradually acquired by those who have been long exposed to infection, and, although during an epidemic few only may escape and the case mortality may reach 90 per cent., yet two or three years will show an abatement in the number and virulence of the attacks, until at last the disease is hardly recognizable by medical men of the pre-Laveran school as anything different to what they call "ordinary malaria." The differential diagnosis from malaria is, as a matter of fact, easy to those who have studied the latter disease and who are accustomed to make a microscopical examination of the blood. Difficulties chiefly arise in diagnosing between kala-azar and cachectic conditions such as general tuberculosis, endocarditis, etc.

The only accurate method of diagnosis in these cases is the examination of blood drawn from the spleen during life. In cases of kala-azar which are recovering parasites may be almost entirely absent even from the spleen.

The Parasite.

The parasite of kala-azar has now been described by so many observers that it is difficult to add anything new regarding its morphology. As generally seen, it is of an elliptical shape, varying in size from $1\frac{1}{2}$ to nearly 4 microns in length by from 1 to $2\frac{1}{4}$ microns in breadth. It varies somewhat in shape, the smaller bodies being more fusiform and the larger ones possessing a more circular outline.

Seen from the side it is distinctly fusiform in section; Christophers has compared it to a closed cockle-shell in general shape. The most striking feature of the parasite is its double nucleus. Nearly all except the smallest bodies show a large oval nucleus at one periphery and a smaller rod-shaped centrosome, placed somewhat at a tangent, on the opposite side of the parasite.

As originally pointed out by Leishman, the arrangement of these two nuclear masses is extremely like that shown in degenerated trypanosomes. (A plate in the *Annales de l'Institut Pasteur* for September, 1901, illustrating an article by Laveran and Mesnil on the trypanosome of the rat, gives an excellent idea of this resemblance.) Stained by Romanowski's method, the parasites appeared to possess a well-marked body wall or capsule. The larger parasites often exhibit vacuoles in the bluish-pink stained body substance.

Christophers has pointed out the fairly frequent occurrence of various developmental forms of the parasite, in which the larger nucleus is seen divided or dividing, and the smaller rod remains undivided.

I have observed these forms and others also in which conjugation appears to be taking place, with a fusion of the larger chromatin masses, while the smaller rods remain separate at opposite sides of the twin parasite.

Large circular cells, with a distinct wall or outline, are

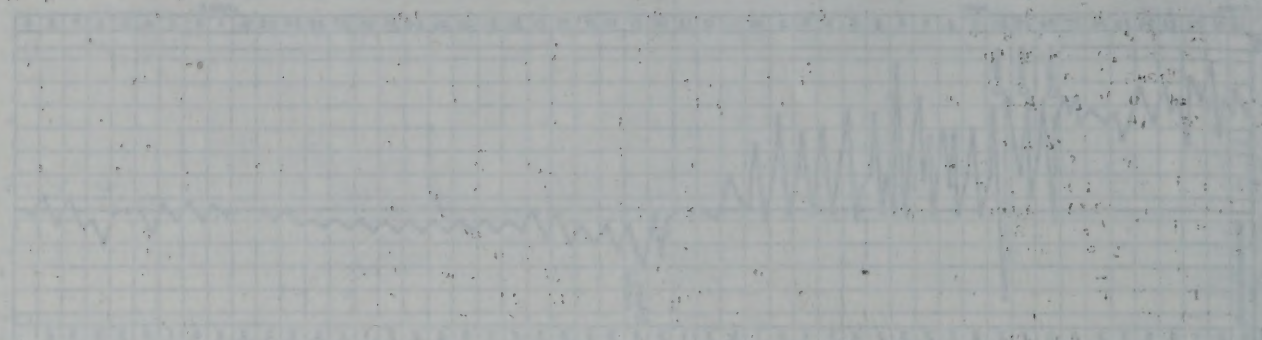


Chart 4.—Case LXV

Case No. 1[illegible]—Mahadavan Nair, aged [illegible] years, a hospital [illegible] from Basleia, Burmah; was admitted very ill on April 4th, [illegible] suffering from continuous fever, between 1[illegible] F. and 1[illegible] F., [illegible] enlarged spleen and [illegible] of the feet and a [illegible] discharge [illegible] both ears. The fever kept more or less continuous till June 4th. [illegible] the morning of that day [illegible] was applied to the axilla, when the temperature [illegible] to an hour to normal, but rose again in the [illegible]. Similar applications of cascade were made on the two [illegible] days, with the same effect of reducing the pyrexia for a short [illegible]. After this the fever became of a marked intermittent type, and [illegible] seemed of [illegible] rigor. During the last week of the pyrexia the [illegible] became gradually [illegible] and weaker, and on May 7th had [illegible] the [illegible] stage. From May 8th to the date of his discharge [illegible] the temperature kept more or less normal. The patient left [illegible] apparently [illegible] had picked up weight, was able to walk [illegible] and eat heartily, and the only sign of disease was a slight oedema of his feet coming on in the [illegible]. This is the only case in which I have [illegible] [illegible] improvement. I am [illegible] it is only [illegible] and expect him back again in a favourable [illegible] fever. This hospital [illegible] is a native of Tellicherry, on the Malabar coast, and [illegible] never [illegible] to be [illegible] in Burmah.

[illegible]—Chas. A. Bentley, M.B.Edin.,

Temporary Assistant.

NOTES UPON KALA-AZAR AND THE NEW PARASITE.

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The Parasite.

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I have observed these forms and others also in which conjugation appears to be taking place, with a fusion of the larger chromatin masses, while the smaller rods remain separate at opposite sides of the twin parasite.

Large circular cells, with a distinct wall or outline, are

frequently to be seen containing what appear to be dividing parasites. These cells vary in size, and contain different numbers of bodies. Some appear to hold only two or three, while others are crowded with twelve or eighteen small-sized parasites. These circular cells or cysts are often to be seen in the protoplasm of large macrophages, in addition to numbers of single parasites.

Situation of the Parasites.

So far I have only found these parasites in the tissues of the spleen, liver, and bone marrow. Manson has, however, detected them in the mesenteric glands, and Christophers has found them in the tissues surrounding ulcers of the colon, and in petechiae in the arachnoid. I have also heard of their being met with within leucocytes in the peripheral circulation, but their occurrence there would appear to be exceedingly rare. A parasite of similar appearance has been shown recently to occur in the tissues of Delhi boil. In an examination of over 60 sores and ulcers in natives of this part of Assam I have not met with this parasite once. An examination of blood drawn from the spleen during life, or of tissue smears obtained *post mortem* from a case of kala-azar, generally shows the parasite to be present in large numbers in large cells, apparently endothelial in character. These cells, however, are evidently phagocytic, and appear to be markedly amoeboid. They are often seen to contain many red blood cells and large numbers of parasites.

I think that Christophers's contention is correct—namely, that the mauve or blue staining stroma or "zooglea mass" which is frequently to be seen enveloping masses of parasites is in all probability derived from these large macrophages, fractured in making the preparation. These so-called zooglea masses are less frequently to be seen in films that have been carefully spread by means of cigarette-paper.

Probable Nature of the Parasite.

At the present time there are, I believe, three suggestions regarding the probable nature of this new parasite.

A. Leishman first suggested that the body was a degenerated trypanosome. I do not think that this idea can be now entertained, as, were it such, we should expect to find recognizable trypanosomes in some part of the human body in cases of kala-azar. Up to the present no observer has reported the discovery of human trypanosomiasis in any part of India. The strong evidence, too, regarding the presence of developmental forms among the new parasites appears to me to entirely negative Leishman's original view.

In connexion with this I should like to suggest that these bodies may be one phase in the life-history of some flagellate. The possibility has struck me in view of certain facts which I have been able to elicitate while investigating the occurrence of kala-azar. It appears that certain species of mud-fish, taken from marshes or bheels adjacent to kala-azar infected lines, in nearly every instance showed marked trypanosomiasis. This has held good in the case of a number of different coolie lines and a kala-azar infected village. Fish obtained from bheels at a distance from any source of faecal contamination, on the other hand, appeared to be entirely free from trypanosome infection. I am now pursuing my investigations on these lines, but up to the present moment have been able to arrive at no definite conclusion.

B. The second theory is that put forward by Professor Laveran, who, shortly after the discovery of the new parasite in cases of fever in Madras by Donovan, pronounced the body to be a species of piroplasma.

I do not think that there are strong grounds for entertaining Professor Laveran's suggestion. The occasional occurrence of a kala-azar parasite superimposed upon a red blood cell does not appear to me to be strong evidence for classing the new parasite among the haemocytozoa. Careful examination of a large number of spleen slides from cases of kala-azar have convinced me that the bluish staining stroma enveloping some of the parasites is not of the nature of degenerated red blood cells. Moreover, I have compared the new parasite with two species of piroplasma canis, to neither of which did it bear the slightest resemblance.

C. The suggestion of Professor R. Ross that the parasite is a tissue parasite of an entirely new genus appears to me to be the most reasonable.

Before admitting this suggestion I think that there are several points to be cleared up. It is true that Manson and Low's idea that the parasite was an example of a class of organism having an exceedingly simple life-cycle has much to recommend it; but I do not think that it has yet been definitely shown that the so-called Leishman-Donovan body is more than the spore of some micro- or myxo-sporidian. I think, also, that the non-parasitic nature of the large macrophages, which so frequently contain the kala-azar body in large numbers, requires to be demonstrated before we can assume that the question is one to be easily settled.

The signs of division and development to be seen in many of the kala-azar bodies is, no doubt, a fact which supports Manson and Low's contention; on the other hand, the enormous number which show no sign of fission or conjugation, and their possession of what appears to be a resistant capsule, are points in favour of their being the spore or endospore of some parasite of a totally different nature.

No doubt the fact that up to the present no "stinging thread" has been demonstrated in the case of any of these bodies is a strong argument against their being the spores of a micro- or myxo- sporidian, but it may yet prove that they are a phase in the life-history of some flagellate or other organism.

The recorded fact of the occurrence of large numbers of endothelial microphages in the capillaries of the spleen and liver in cases of splenic anaemia and Banti's disease seems to negative the idea that these large amoeboid cells are of a parasitic nature, unless the Leishman-Donovan body is subsequently demonstrated in those conditions. The occurrence of similar large cells in the tissues in cases of malaria and trypanosomiasis are also points against the theory, but the finding of malarial pigment in one of them, as recorded by Christophers, does not appear to have any bearing on the point at issue, for it is a well-known fact that foreign bodies of all sorts may be recognized in the body substance of several varieties of amoeba coli, and there is no reason, imagining for the sake of argument that the macrophages are themselves parasites, that they should not as readily engulf red blood cells containing malarial parasites as well as any other.

Although the staining reaction of these large cells is in nowise characteristic, resembling that of the large lymphoid elements, this is hardly a strong point against the suggestion of their parasitic nature, as it may be well to remember that one at least of the several species of amoeba to be found in the intestines of man in this part of India has a staining reaction very similar to that of these cells. It is also known that the pseudo-leucocytes that are present in the blood in trypanosomiasis and spirillar fever have a similar staining reaction to elements of normal blood.

Mode of Entrance and Exit of the Parasite.

As Manson has already pointed out, it is of importance that we should endeavour to learn the mode of entrance and exit of the parasite to and from the human body. So far, I believe, all attempts at finding the parasite outside the human body have proved useless.

In the course of a long series of investigations, suggested to me privately by Sir Patrick Manson, I have carefully examined the blood and tissues of a large number of animals of various kinds, in the hope of finding some clue. I have been unsuccessful in finding the parasite in dogs, cats, goats, cattle, rats, deer, bats, fish, frogs, and snakes. The examination of the stomach and salivary glands of mosquitos has likewise been fruitless, and the dissection of several species of blood-sucking flies has not shown any result.

This latter operation is exceedingly difficult, and it is possible that greater experience may show other results. Tabanidae and stomoxys are exceedingly common in this part of Assam, and give great annoyance to the natives during the rainy season. As part of a routine examination I have not neglected to search well and hoolah (marsh) water for the parasite.

Samples of surface and bottom water have been centrifugalized, and the resulting deposit carefully stained and examined under the microscope, but so far without result. The search for the mode of exit has likewise up to the present been no more successful. The search through stained slides prepared from the faeces of kala-azar patients has only brought to light the fact that this class as a whole exhibit an extraordinary number of protozoal organisms of different kinds among the miscellaneous fauna of their intestines. Four different varieties of amoeba have been recognized, besides cercomonas and a peculiar organism provided with a ciliated membrane, apparently distinct from paramaeceum coli.

One or more cases of kala-azar exhibited a body which appeared to be a coccidium, very different from those described by Giles. This body resembles in general shape a closed mussel shell; in size it is about 12 to 15 microns long, by about 7 or 8 broad. It appeared to be enclosed in a

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refractile capsule. The stools from healthy people in this district, while showing the presence of two species of amœbæ in small numbers, together with the usual number of ova of various worms common to all natives of this part, were otherwise fairly free from protozoal organisms. I may mention here that I have also examined a certain number of ankylostomata expelled by vermicides from the intestines of cases of kala-azar. In one instance, among the blood cells contained in the alimentary tract of one of the worms, a binucleated body resembling the parasite of kala-azar was found. In two instances also, while examining slides from a case of kala-azar exhibiting dysenteric symptoms, bodies of this description were also seen.

Urine from cases of kala-azar, centrifugalized and the deposit examined, showed nothing of interest. Sputum from cases of the disease likewise failed to show more than the usual collection of bacteria common to cases of bronchial catarrh, etc. Slides prepared from several cases of kala-azar who had developed cancrum oris petechial eruptions have shown nothing beyond bacteria.

As I have previously mentioned, I have so far failed to find the parasite in any skin lesion among the natives here. Although some of the less cleanly natives suffer much from skin affections superficially resembling Delhi boil, I have up to the present failed to meet with this disease in Assam.

Major Donovan has announced the finding of the kala-azar parasite in the lesions of scabies upon individuals suffering from infection with the parasite of kala-azar. Up to the present I am unable to confirm this occurrence in cases in this district.

Further investigation may show some connexion between the local skin lesion and the general infection; but, so far, known facts appear to indicate the existence of two different species of parasite of the same genus. Were skin lesions to be the initial mode of infection, one would expect to find a frequent implication of the superficial lymphatic glands—a symptom which up to the present remains unrecorded in cases of kala-azar.

Conclusion.

It appears to me that the clinical history and the epidemiology of kala-azar give certain indications as to necessary lines of research.

It has been my experience during the four years in which I have been familiar with the disease that cases suffering from severe fever appeared to be more dangerous, as far as the spread of the epidemic went, than those whose temperature was more frequently near the normal.

It is these cases with high and continued fever who show on splenic puncture a larger proportion of fission and conjugation forms than the milder type of case.

Again, I have frequently noticed when the epidemic was at its height that cases which showed dysenteric symptoms, and especially those who became bedridden while suffering from dysentery, were sure to be followed by fresh cases in the same household or among the attendants.

When the intestinal form of the disease is in abeyance, the epidemic gradually assumes a milder type, with a corresponding decrease in the case mortality.

Another fact which appears to me to be of importance in regard to any investigation of the disease is the comparative immunity of Europeans. Although isolated cases are met with in Europeans, they are uncommon. This fact appears to indicate that certain conditions are necessary for the spread of the disease to which Europeans as a class are rarely exposed; and therefore the careful study of the case history of such patients when they are met with may be expected to give a valuable indication regarding the source of infection.

V.—Lieutenant S. R. CHRISTOPHERS, I.M.S. (on Special Duty).

TROPICAL SPLENOMEGALY AND ORIENTAL SORE.

WHOEVER may have first seen the parasitic bodies variously known as the Leishman-Donovan bodies—piroplasma donovani, leishmania, or helcosoma—it is undoubtedly chiefly owing to the researches of Donovan that the occurrence of an entirely new parasitic disease of man was first brought to the attention of parasitologists and students of tropical medicine generally. With Donovan's discovery of the disease in Madras and Laveran's definite announcement of the parasitic nature of the bodies, speculation at once became rife regarding their zoological position, life-history, and method of transmission.

The earliest researches centred chiefly around the morphology and the zoological affinities of the bodies. They were thought by Leishman to be flagellates, on account of the conspicuous chromatin masses, which certainly appear to represent a karyosome and centrosome very like those of the trypanosomata. But that they are any form of degenerated trypanosome is exceedingly unlikely in the face of the large number of recorded cases in which no trypanosomes have been present. The same unlikelihood pertains to their supposed affinities with the genus piroplasma, and the discovery by Wright of the bodies crowded in the cells of granulation tissue in tropical ulcer would appear to be the death-blow to this view. It has been suggested that the bodies are of the nature of microsporidia, but the proof for this rests on no further evidence than their remarkable uniformity in size and appearance. On the data we have at our disposal, it is indeed impossible to place these bodies in any of the genera or better known divisions of the sporozoa. A good deal of speculation has raged around the nature of the so-called "matrix" of Ross, "zooglea mass" of Manson, and "red corpuscle" of Laveran. In my first report I gave reasons for considering this nothing more or less than the cytoplasm of endothelial cells of the spleen, more especially that derived from the large macrophages which bud and vacuolate so as to give rise to the curiously definite masses in question. The process is much increased by the fluid usually present in the barrel or needle of the syringe used for puncture. A study of sections shows very clearly the real condition, which is one of endothelial cells gorged with the parasites.

In regard to the nature of the infective process, it has very generally been taken for granted that the recently discovered parasite is a blood parasite, much in the sense that the malarial parasite is. If Laveran should be right in his surmise that the parasite is a species of piroplasma, this will of course be true. As matters stand at present, the parasite does not appear to be related to this genus or to be a parasite at any time of the red cell.

Are they to be considered as parasites of the plasma? On this point I have no hesitation in saying, from the result of my recent researches, that they are probably a blood parasite in no other sense than are the organisms of septicaemic infection or the tubercle bacillus.

While the attention of many observers was still directed to the novelty of the presence of the bodies in the spleen and liver of cases of tropical splenomegaly, Wright, in America, had, apparently independently, discovered the same bodies in large numbers in the granulation tissue of tropical ulcer, a lesion which had long been recognized as probably a specific local granuloma. That the bodies described by Wright are identical with those found in cases of enlarged spleen in Madras cannot be doubted after a study of the excellent photographs which accompany his paper. We also have the important communication from Captain James, I M S., that abundant forms indistinguishable from those in the Madras cases and in kala-azar from Assam were found by him in cases of Oriental sore from North India. The general pathology of the lesion and the relation of the bodies to the tissues as described by Wright make it seem certain that in this case the newly discovered parasite is acting as the causal agent in a focal granuloma of the skin.

Shortly after Wright's paper reached India, Donovan found the characteristic bodies in small numbers in ulcers in an advanced case of the Madras disease with enlarged spleen and cachexia. Stimulated by the discoveries of Wright and Donovan, I examined very thoroughly the tissues of fatal cases of the disease, especially with reference to the skin and intestinal lesions found in such cases. The result has been to throw a considerable amount of light on the nature of the infective process.

Bodies were found in the spleen, liver, and bone marrow, intestine, lungs, testis, and kidneys. I have in the first report already shown that the apparently free forms seen in specimens of splenic blood cannot be considered as other than forms artificially liberated by rupture of cells, more especially the large macrophages. The same relation holds good in the case of the liver and bone marrow, and in all the organs the condition may be described as an engorgement of the endothelial cells with the parasite. In the lung, testis, and kidney, bodies were much less numerous, but were in places readily seen lying in cells of endothelial nature. Free forms were never seen in sections.

In unulcerated papules of the skin, in small and large ulcers of the skin and of the intestine, the bodies were consistently present. They were as a rule scattered singly through the

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tissue, and appeared to be lying embedded in the cytoplasm of tissue cells. Closer investigation showed that they lay in the endothelial cells of the finest capillaries. No bodies were ever detected lying free in the lumen of vessels. In larger vessels, in the immediate neighbourhood of granulation tissue, endothelial cells were seen containing from two to six bodies, and in many of the still larger ones cells crowded with bodies almost blocked the lumen.

Briefly stated, we have in infection by the Leishman-Donovan bodies a type of infection in which the vascular endothelium is mainly implicated. The importance of such a fact is manifest. In the first place, it suggests the comparison of the Madras disease (chronic malarial cachexia) with the usual type of septicaemia. In this, from the researches of Werigo[1] and Kuhnan[2], it is evident that infection of the blood stream with the septic organism is chiefly shown by the deposit of forms in the endothelium and leucocytes of the viscera. If, indeed, we say that the disease seen in Madras is a systemic infection of septicaemic type, we shall most nearly express what is known as to the nature of this new protozoan disease. This view will also allow us to see in Oriental sore a local infection by the same organism.

As regards the cycle of development of the parasite, we believe that multiplication of forms is mainly by binary fission, the larger fission forms being of secondary importance. The parasites having entered or been taken in by an endothelium cell, would appear to proliferate, causing eventually the disruption of the cell and the temporary setting free into the blood stream of the crowd of contained bodies. There does not appear to be any intracellular digestion of forms included in the endothelium cell, and this latter very probably constitutes a suitable host for the parasites, in spite of the fact that it may originally take them in by reason of its phagocytic properties.

VI.—ALDO CASTELLANI, M.D. Florence,
Director, Bacteriological Institute, Colombo, Ceylon.

"LEISHMANIA DONOVANI" IN CEYLON.

To my knowledge Leishman-Donovan bodies have been found so far only in cases with well-marked features of tropical splenomegaly. It may be of some interest, therefore, to record a case in which these bodies were present, but in which symptoms were practically absent, the case being probably at the very beginning of the disease.

D. S., Cinghalese, aged 20, was for a few days in the General Hospital of Colombo under care of Dr. Sinnatamby. The patient was affected with lobar pneumonia, and showed all the usual symptoms of that disease. He died on May 4th, 1904, at 6 a.m. I held the *post-mortem* examination at 11.45 a.m. of the same day. The body was in a fairly good state of nutrition. No cutaneous eruptions, no bedsores. Rigor mortis present.

Thoracic Viscera.—Parietal pericardium had a normal appearance. Pericardial fluid not increased. The heart slightly enlarged, valves normal. Right lung healthy. The whole lower lobe of left lung consolidated, airless; the pleural surface showed a fibrinous exudate; cut surface dark red, with a granular appearance.

Abdominal Viscera.—No effusion in the peritoneal cavity. Liver enlarged, signs of fatty degeneration. Spleen somewhat enlarged, but not hard; no signs of perisplenitis: cut surface of a vivid red; pulp soft. Kidneys both slightly enlarged and congested. Pancreas healthy. Intestine normal; no entozoa.

From the spleen as a matter of routine I made two smears. The films were stained some hours later in the Bacteriological Institute according to Ziemann's modification of Romanowsky's method. Both films presented a very large number of Leishman-Donovan bodies. I was surprised, as the *post-mortem* examination of the body had not shown the features of a splenomegaly. The bodies were well stained and identical with those I have seen in the preparations of Donovan, Manson, and Low. In my films the free forms were most abundant; some embedded forms were also present, though as a rule, according to some authors, the embedded varieties are found generally in preparations made *intra vitam*. I could not see any intracorpuscular forms, as described by Laveran and Mesnil; a few parasites could be seen superposed or underlying a red blood corpuscle. I was especially struck with the large number of leucocytes, the nuclei of which contained deeply-stained masses resembling closely Leishman-Donovan bodies. In fact, 15 per cent. to 25 per cent. of the mononuclear as well as of the polymorphonuclear leucocytes presented such masses stained a deep red-purple in their nuclei.

Ross has already called attention in one of his papers to the presence of some curious massive nodular deeply-staining granules arranged principally round the periphery of the nucleus of leucocytes. Ross states that he is not familiar with such granules, and cannot definitely connect them with the Leishman-Donovan body.

Ross observed such a peculiar appearance of the leucocyte nuclei in preparations made during life; my preparations were made after death, but it is to be noted that the *post-mortem* examination was held less than six hours after death. Laveran and Mesnil also state that in some cases they have had the impression of seeing the Leishman-Donovan bodies included in the nuclei of the leucocytes, and that in such cases the nuclei always presented some changes.

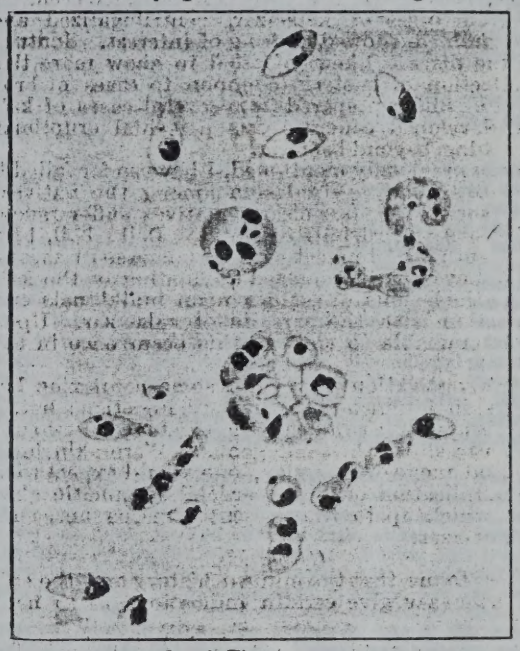

Fig. 1.

It seems to me that, as already practically proved by Manson, Ross, and Low, the Leishman-Donovan bodies are not piroplasmata. They are not likely to be degenerated trypanosomata, seeing that no observer has found stained flagella, though smears from the spleen of rats infected with

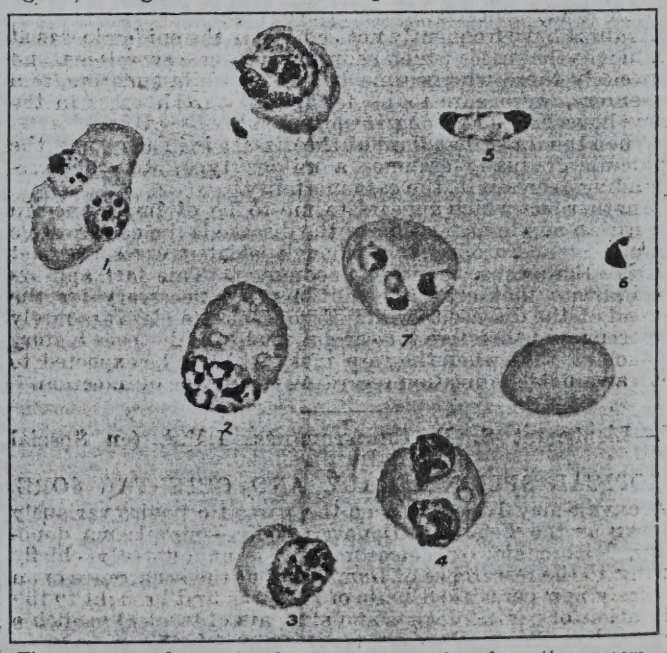

Fig. 2.—1, 2, 3, 4, leucocytes showing in the nucleus formations resembling the Leishman-Donovan bodies; 5, 6, free forms; 7, embedded forms.

T. lewisi, as pointed out by Leishman, present peculiar formations very much like the Leishman-Donovan bodies. In

[1] *Annal. Institut Pasteur*, 1892.
[2] *Zeit f. Hygiene*, Bd. 25, p. 492.

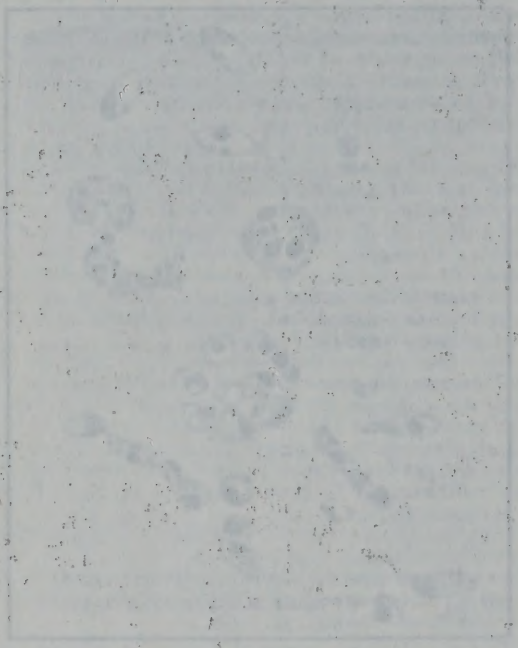

Fig. 4.

It seems to me that, as already practically proved by Manson, Ross, and Low, the Leishman-Donovan bodies are not piroplasmata. They are not likely to be degenerate trypanosomata, seeing that no observer has found trained flagella, though smears from the spleen of rats injected with

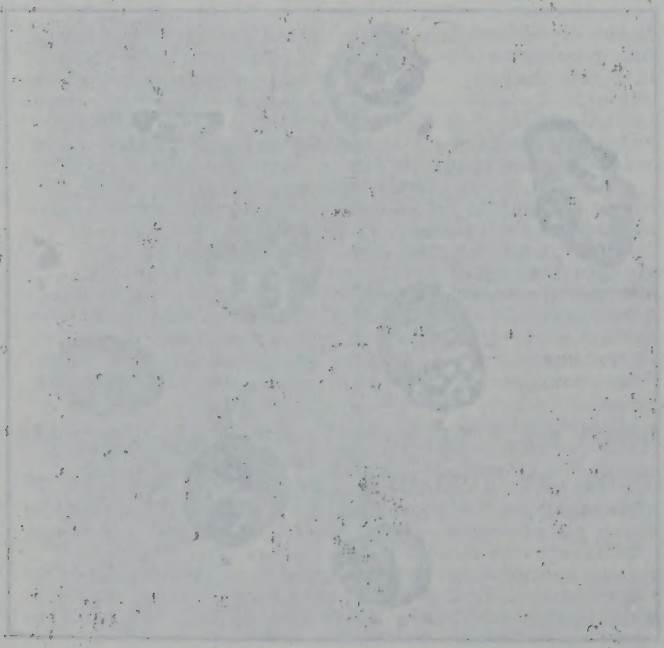

Fig. 4.—1, 2, 3, 4, leucocytes showing in the nucleus formations resembling the Leishman-Donovan bodies; 5, 6, free forms; 7, embedded forms.

T. lewisi, as pointed out by Leishman, previous peculiar formations very much like the Leishman-Donovan bodies. In

Ceylon, as observed by Dr. Willey and myself, 20 per cent. to 30 per cent. of rats are infected with T. lewisi. Smears from the spleen of such rats show structures very much like the Leishman-Donovan body. It is much more probable that the Leishman-Donovan body represents a new genus (Leishmania). As the nuclei of the leucocytes, at least in the preparations examined by me, show so often masses resembling the Leishman-Donovan body, could it not be that the parasite in one of its stages of development is a parasite of the nucleus of the leucocytes—a leucocytozoon?

It is remarkable that leucocytes presenting in their nucleus Leishman-Donovan bodies, or formations resembling these, are far more numerous than are the leucocytes with similar structures lying in their protoplasma. It is remarkable also that some nuclei appear as if they had been damaged and sometimes almost destroyed by those bodies. All this cannot be explained in my opinion by phagocytosis.

In the lower animals some parasites of the nuclei of the leucocytes have been described already by Danilewsky, Klemann, Berestneff, etc. It must be stated, however, that these parasites (leucocytozoon, Danilewsky, etc.) morphologically have no resemblance to Leishmania-Donovani. The view I give I bring forward merely as a suggestion.

In conclusion my case may perhaps be of some value:

1. In connexion with the geographical distribution of the parasite, the Leishman-Donovan body had not hitherto been observed in Ceylon.

2. The case was not a typical case of tropical splenomegaly; probably it was a case at the very beginning of the disease; the intercurrent disease (lobar pneumonia) killed the patient.

3. The examination of my preparations confirms the opinion of Manson, Ross, Low, etc., that the bodies are not intracorpuscular parasites of the red blood corpuscles.

VII.—Llewellyn Phillips, M.D., F.R.C.S., M.R.C.P.,
Kasr el Ain Hospital, Cairo, Egypt.

NOTE ON THE OCCURRENCE OF THE LEISHMAN-DONOVAN PARASITE IN ARABIA AND EGYPT.

Enlargement of the spleen, with or without ascites, is a very common disease in Egypt, and for some time I have been studying the cases of ascites that occurred in Kasr el Ainy Hospital, the results of which will appear in the forthcoming volume of the records of the Egyptian Government School of Medicine. The main facts that I elicited were that in 100 consecutive cases of ascites, diseases of the heart accounted for 4 (possibly 7) per cent., of the lungs 3 per cent., of the kidneys 8 (possibly 9) per cent., of the peritoneum 3 per cent., of the liver and spleen 7 or 8 per cent., of which malignant diseases formed 5 per cent. of the whole, syphilis 1 per cent., alcohol 8 per cent., bilharzial cirrhosis 1 or 2 per cent., malaria 30 per cent., leaving 32 per cent. of doubtful etiology. I had, however, hesitated to puncture enlarged spleens in these cases in order to search for malarial parasites. But in April of this year Dr. Balfour of Khartoum told me that in a case at Khartoum, on splenic puncture Leishman's parasite had been discovered. On being assured that no ill effects usually followed puncture of the spleen, I decided to search for the parasite in cases under my care at Kasr el Ain Hospital, feeling fairly certain that some of these cases of enlargement of the spleen without any apparent cause would turn out to be associated with the parasite in question. This I accordingly did, staining the films so obtained by Leishman's stain, or by Romanowsky's stain, prepared as recommended in the report of the Trypanosomiasis Commission.

After some failures, I found the parasite in large quantities in the splenic pulp of a Turk who had lived for a long time in Yemen, in Arabia. Three days later I admitted another patient who had also lived for a long time at Mecca, in Arabia, and whose splenic tissue also yielded the body in question in very large numbers. These bodies, in one of the two cases, were perfectly typical, occurring often in masses of 200 to 300, and staining with the Romanowsky red, and with the red of Leishman's stain. In the isolated parasites the two chromatin bodies could be made out. I showed the films to Dr. Bitter, of the Sanitary Department, Cairo, and he recognized in them the same bodies that he had been shown by Dr. Sheffield Neave in the case from Khartoum. A few days later I took in an Indian from Delhi, with an enlarged spleen, and in him I also found bodies identical with the other two cases. (Details of these cases follow.)

We must therefore add Arabia to the countries in which this parasite occurs, and since the Hedjaz is the place of pilgrimage of the whole Mohammedan world, we may have to reckon with a parasite of great import. Further, it has been found in Delhi boil; it may also be found in the Aleppo boil of Arabia.

Taking into consideration its occurrence in Arabia and the great prevalence of chronic enlargement of the spleen in Egypt one would not be surprised at finding it also in the dwellers of this country. This surmise has proved correct; I have since found it in a native of the Menufieh province of Egypt, the body occurring in fair numbers. I have also found it in another case of a native Egyptian, in small numbers.

My house physician, Dr. Iscandar, who has helped me in the preparation of the films, has pointed out to me that in the cases in which the parasite has occurred, splenic puncture has been followed by a rise of temperature, but in cases in which it has not been found, no such rise has taken place.

As the following short notes show, the clinical aspects of the cases closely agree with the clinical aspects of the cases described in India.

1. Abdu Rashid, a Turk, aged 30, was admitted into Kasr el Ain Hospital on June 16th, 1904, complaining of pain after food and giddiness on slight exertion, constipation, and the occasional passage of a few drops of blood after defaecation. He had lived for the last two years in Yemen, in Arabia. He states that a month and a half ago he had an attack of diarrhoea with tenesmus and blood in the stools; this stopped under treatment. About the same time he had an attack of fever which began with rigors and which lasted during the period of the diarrhoea. The physical examination revealed that he was anaemic. His spleen was enlarged, reaching nearly to the umbilicus, the extent of the enlargement below the ribs being 7 cm. No malarial parasites were found in the blood. The blood count showed anaemia. There was nothing else worthy of note in his physical examination. During his stay in hospital his temperature ranged from 36° to 37° C., and rose after splenic puncture to 38.5° C. The parasites occurred in large numbers in his splenic pulp.

2. Hassan Mohammed el Naggar, an Egyptian, aged 35, was admitted into Kasr el Ain Hospital on June 19th, 1904, with oedema of the legs. The patient had lived for the last fifteen years in the Hedjaz, in Arabia. For the last two years he had suffered from attacks of fever characterized by rigors and ending with sweating. During this same period he had also had irregularity of the bowels with occasional tenesmus and passage of blood. He was emaciated, anaemic, and had oedema of the lower extremities. This latter had been present for three months. His spleen was found to reach 6 cm. below the ribs in the nipple line. The liver could also be felt enlarged. There was a systolic murmur to be heard over the cardiac area, and he passed daily 3,000 to 5,000 c.cm. of urine of low specific gravity. His temperature was irregular, ranging from 36° to 38° C., and during the first twelve days of his stay in hospital he had diarrhoea. The parasites were abundant in his splenic pulp.

3. Ahmed el Zanati, aged 30, an Egyptian from the province of Menufieh, in Lower Egypt; occupation, fellah. He was admitted to Kasr el Ain Hospital on June 30th, 1904. For the last six months he has had attacks of fever, the fever coming on every evening and lasting four days, and then subsiding without treatment. During the attacks he used to feel pain in the left side and in the lower part of the abdomen. Three months ago he noticed distension of the abdomen coming on, and he became unable to do any manual work. At the beginning of the illness there was looseness of the bowels, blood also was passed in the motions, and defaecation was accompanied by tenesmus. The physical examination revealed anaemia; this was accompanied by a soft systolic murmur over the mitral and pulmonary areas. There was slight oedema of the feet. The spleen was enlarged, and extended 6 cm. below the ribs. There were no signs of free fluid in the abdominal cavity. Splenic puncture, as already stated, revealed the organism in fair quantities. His temperature during his stay in hospital ranged from 36° to 38° C., rising to 38° C. and to 37.5° C. after splenic punctures. There was slight looseness of the bowels during his first few days' stay in hospital.

4. Ibrahim Rakah, aged 14, an Egyptian from the Gharbieh province of Lower Egypt, a fellah, was admitted to Kasr el Ain Hospital on July 4th, 1904. Two years ago he was attacked by fever; there were three separate attacks, each lasting about a week, and characterized by a rise of temperature in the afternoon, preceded by shivering and followed by sweating. He was anaemic (3,000,000 red blood corpuscles being present), and examination revealed a systolic murmur over the mitral area. The spleen was enlarged, reaching 10 cm. below the ribs, and the liver was also enlarged, reaching 6 cm. below the costal margin. Splenic puncture yielded blood containing but few organisms, but these were present in sufficient number to be sure of their presence. In him also the temperature rose after splenic puncture, reaching 37.8° C. There was some looseness of the bowels during his first few days' stay in hospital.

VIII.—Sir Patrick Manson, K.C.M.G., F.R.S., D.Sc.

Sir Patrick Manson said: It is certain that many medical men will be exploring spleens for Leishman-Donovan bodies. It is not an operation free from danger. One danger specially likely to be encountered, on account of a leading symptom, is the possibility that the splenomegaly and febrile attacks of leucocythaemia may be regarded as kala-azar, and the

as observed by Dr. Whitney and myself, as per cent. to [illegible] of vast are infested with it. Swarms from [illegible] of such a show attributing very much like the [illegible] Dionyson body. It is much more probable that [illegible] Dionyson body represents a new genus (Leuk[illegible]). As the nucleus of the leucocytes, at least in the pre[illegible] examined by me, allow so often massing resembling [illegible] Dionyson body, could it not be that the parasite [illegible] of the stage of development is a parasite of the [illegible] of the leucocytes—a leucocytozoon.

[illegible] is remarkable that leucocytes present in their nucleus [illegible] Dionyson bodies, or locomotions resembling these, are [illegible] numerous than are the leucocytes with similar [illegible] lying in their protoplasm. It is remarkable also [illegible] cells must appear as if they had been damaged and [illegible] almost destroyed by these bodies. All this [illegible] explained in my opinion by phagocytosis.

[illegible] the lower animals some parasites of the nuclei of the [illegible] have been described already by Danilewsky, [illegible] Bevistedt, etc. It must be stated, however, that [illegible] parasites (monocytozoon, Danilewsky, etc. Jungbolot) [illegible] have no resemblance to Leishmann-Donovan. The [illegible] I give it being merely as a suggestion.

[illegible] may perhaps be of some value:

[illegible] in connexion with the geographical distribution of the [illegible], the Leishmann-Donovan body had not hitherto been observed in Egypt.

[illegible] case was not a typical case of tropical splenomegaly; [illegible] it was a case in the very beginning of the disease; [illegible] intermittent disease, probably simulated the patient. [illegible] the examination of my preparations confirming the [illegible] of malaria. Hence, now, since the bodies are not [illegible] particular parasites of the red blood corpuscles.

VII.—LEWERENZ BEY, M.D., F.R.C.S., M.R.C.P.,
Kasr el Ain Hospital, Cairo, Egypt.

NOTE ON THE OCCURRENCE OF THE LEISHMAN-DONOVAN PARASITES IN ANEMIA AND SCURVY.

[illegible] of the spleen, with or without anemia, is a very common disease in Egypt, and for years since I have been [illegible] the cases of anemia that occurred in Kasr el Ain Hospital, the results of which will appear in the forthcoming [illegible] of the records of the Egyptian Government School of Medicine. The main facts that I allotted were that in the [illegible] cases of malaria, diseases of the heart accounted [illegible] (possibly 7) per cent., of the lungs 3 per cent., of the [illegible] (possibly 9) per cent., of the peritoneum 3 per cent., [illegible] the liver and spleen 3 per cent., of which malignant [illegible] formed 3 per cent. of the whole, syphilis 1 per cent., [illegible] 8 per cent., kidney disease 1 or 2 per cent., [illegible] 10 per cent., leaving 12 per cent. of doubtful etiology. [illegible], however, hesitated to pronounce enlarged spleens in these cases in order to search for malarial parasites. But in [illegible] of this year Dr. Blanc of Khartoum told me that in a [illegible] of Khartoum, on splenic puncture Leishmann's parasite [illegible] been discovered. On being assured that no ill effects [illegible] followed puncture of the spleen, I decided to search [illegible] the parasite in cases under my care at Kasr el Ain Hospital, feeling fairly certain that some of these cases of enlargement of the spleen without any apparent cause would [illegible] out to be associated with the parasite in question. This [illegible] accordingly did, obtaining the sins so obtained by Leishmann's stain, or by Jenner-Giemsa's stain, prepared as recommended in the report of the Trypanosomiasis Commission.

After some failures I found the parasite in large quantities [illegible] the spleen pulp of a Turk who had lived for a long time [illegible] Tenan, in Arabia. Three days later I obtained another [illegible] patient who had also lived for a long time at Moca, in Arabia, and whose spleen also yielded the body in question in [illegible] large numbers. These bodies, in one of the two cases, [illegible] particularly prominent, occurring often in masses of 20 to 30, staining with the Giemsa-Leishmann red, and with the red of Leishmann's stain. In the isolated parasites the two chromatin bodies could be much [illegible]. I showed the films to Dr. Bilharz, of the Bacteriology Department, Cairo, and he recognized in them the same bodies that he had shown by Dr. Sheffield Neave to the case from Khartoum. A few days later I took an ice-lad on from Dahab, with an enlarged spleen, and in this I also found bodies identical with the other two cases. (Details of these cases follow.)

We need discuss the question as to the countries in which this disease occurs, and since the Sudan is the place of [illegible] of the whole Mohammedan world, we may

bury to reckon with a parasite of great importance. Perhaps it has been found in Darfur too; it may also be found in the Abyssinian hill of Arabia.

Taking into consideration the occurrence in Arabia and the great prevalence of chronic malaria-cases of the spleen in Egypt one would not be surprised at finding it also in the dwellers of this country. This surmise has proved correct; I have alone found it in a native of the Menufieh province of Egypt, the body occurring in fair numbers. I have also found it in another case of a native Egyptian, in small numbers.

My house physician, Dr. Jacundar, who has helped me in the preparation of the films, has pointed out to me that in the cases in which the parasite has occurred, splenic puncture has been followed by a rise of temperature, but in cases in which it has not been found, no such rise has taken place.

As the following short notes show, the clinical aspects of the cases closely agree with the clinical aspects of the cases described in India.

1. Abdo Hassib, a Turk, aged 20, was admitted into Kasr el Ain Hospital on June 4th, 1903, complaining of pain after food and gives an slight exertion, constipation, and the occasional vomiting of a few drops of blood after defaecation. He had lived for the last two years in Yemen, in Arabia. He states that a month and a half ago he had an attack of diarrhoea with tenesmus and blood in the stools, which stopped under treatment. About the same time he had attacks of fever which began and which lasted during the period of the diarrhoea. The physical examination revealed that he was anemic, his spleen was enlarged, reaching nearly to the umbilicus, the edge of the enlargement below the rib being 7 cm. in radial measure. There was no [illegible] in the blood. The blood count showed anemia. There was no [illegible] other evidence of loss in the digestive apparatus. During his stay in hospital his temperature rose and fell, 96° to 99° C., and was also [illegible] to 38° C. The paroxysms occurred during anemia in his spleen pain.

2. Hassan Mohammed el Hegeg, an Egyptian, aged 32, was admitted into Kasr el Ain Hospital on June 9th, 1903, with cachexia of two years. The patient had lived for the last three years in the Sudan, in Arabia. For the last two years he had suffered from malaria, or fever simulated by rigors and sudden with sweating. During this same period he had also had irregularity of the bowels with occasional tenesmus and passage of blood. He was emaciated, anemic, and had edema of the lower extremities. This latter had been present for three months. This spleen was found to reach 6 cm. below the rib in the radial line. The liver could also be felt enlarged. There was a systolic murmur to be heard over the cardiac area, and he passed daily urine to some [illegible] of urine of low specific gravity. The temperature was [illegible], ranging from 96° to 99° C., and during the first twelve days of his stay in hospital he had diarrhoea. The paroxysms were about last in the morning.

3. Ahmed el Ismail, aged [illegible], an Egyptian from the province of [illegible], in Lower Egypt; complaint, ague. He was admitted to Kasr el Ain Hospital on June 9th, 1903. For the last six months he has had attacks of fever, the fever coming on every evening and lasting four days, and then subsiding without treatment. During the attacks he used to feel pain in the left side and in the lower part of the abdomen. There months ago he noticed distension of the abdomen coming on, and he became unable to do any manual work. At the beginning of the illness there was hoarseness of the bowels, blood also was passed in the motions, and defaecation was accompanied by tenesmus. The physical examination revealed anemia; this was accompanied by a soft systolic murmur over the mitral and pulmonary areas. There was slight edema of the feet. The spleen was enlarged, and extended 6 cm. below the rib. There were no signs of free fluid in the abdominal cavity. Splenic puncture, as already stated, revealed the parasites in large quantities. The temperature during his stay in hospital ranged from 96° to 99° C., rising to 104° C. and to 99° C. after splenic puncture. There was slight hoarseness of the bowels during his first few days' stay in hospital.

4. Hassan Kasab, aged [illegible], an Egyptian from the Dakahlieh province of Lower Egypt, a fellah, was admitted to Kasr el Ain Hospital on July 4th, 1903. Two years ago he was attacked by fever. There were fever paroxysmal attacks, each lasting about a week, and alternated by a rise of temperature on the alternate, preceded by shivering and followed by sweating. The fever became continuous, and other symptoms being present, and examination revealed a soft systolic murmur over the mitral area. The spleen was enlarged, reaching to the, below the rib, and the liver was also enlarged, reaching 4 cm. below the costal margin. Splenic puncture yielded blood containing out few organisms, but these were present in sufficient number to be sure of their presence. In this case the temperature rose after splenic puncture, reaching 104° C. There was some hoarseness of the bowels during his first few days' stay in hospital.

VIII.—Sir Patrick Manson, K.C.M.G., F.R.S., D.Sc.

Sir Patrick Manson said: It is certain that many medical men will be exploring spleens for Leishman-Donovan bodies. It is not an operation free from danger. The danger especially likely to be encountered, on account of a leading symptom, is the possibility that the splenomegaly and leucocytosis may be regarded as kala-azar, and the

spleen punctured with disastrous haemorrhage. Therefore I would urge blood examination before splenic puncture. A matter of great practical importance is the settlement of the way of exit and the way of entrance of the parasite. Its association with ulcerations, dysentery, and oriental sore, suggest that it emerges through ulcerations and enters by insect bites. Oriental sore must now be regarded as a serious disease, as sometimes leading to a general infection. Thus, I have seen a patient who suffered from oriental sore, and subsequently became the subject of disease of the testes, supposed to be tuberculous, for which he was castrated.

IX.—DAVID BRUCE, C.B.,
Colonel, Royal Army Medical Corps.

COLONEL BRUCE said: I have listened with the greatest interest to Major Leishman's and the other papers on this newest and apparently most important of diseases—kala-azar—and I think this Section may congratulate itself upon the important work which has been brought before it this morning. To me, one of the most interesting of the experiments brought forward is that by Captain Rogers on the development of Leishman's bodies into trypanosoma—*in vitro*. The experiment was on the simplest lines. I understand he simply placed a few drops of citrated splenic blood in a test tube and kept it at 22° C. In a short time beautiful fully developed trypanosomata were found to be present. It sounds like a fairy tale, and yet it is difficult to see where a fallacy could have crept in. He states he was working with sterilized solutions. We know flagellate organisms will sometimes develop from tap-water. I heartily congratulate Captain Rogers on this startling observation, and await eagerly its confirmation. In the second place, I would like to call attention to the nomenclature of these bodies. Lately I find them called the Cunningham-Leishman-Donovan bodies, and usually they are called the Leishman-Donovan. Now, as I understand this subject, this brilliant observation of the presence of these bodies in the spleen of cases of this disease was made by Leishman, and by Leishman alone. Donovan only confirmed the observation, as many others have done. It would be just as logical to call these bodies the Leishman-Donovan-Ross-Bentley-Manson-Low, etc., bodies, as Leishman-Donovan. I do not suppose it is Donovan's fault that this honour has been thrust upon him, it is rather a case of being saved from one's friends.

X.—G. C. LOW, M.B.Edin.,
Superintendent, London School of Tropical Medicine.

DR. LOW said: In reply to Colonel Bruce's remarks on Captain Rogers's experiments on the production of trypanosomes from cultures of Leishman-Donovan bodies, I may state that, in the case Sir Patrick Manson and I described from the London School of Tropical Medicine, cultures were attempted. Tubes of haemoglobin agar and haemoglobin broth were inoculated with splenic blood and incubated, some at 37° C., others at room temperature. In neither of those did the parasites multiply, and on the second day had entirely disappeared. Similarly, fresh specimens, ringed with vaseline and watched under the microscope for four days, showed no movements in the parasite and no sign of development. Our experiments, however, were, perhaps, too few to be considered in any way conclusive. In regard to the pathology of this disease, many of the previous speakers have used different terms as regards the cells of the body in which the parasites are found. I think it is important that the exact site should be thoroughly determined. They are found in the macrophages, or splenic cells of the spleen, in the secreting cells of the liver, in the marrow cells, and also apparently in some situations in the endothelial cells. Experiments on monkeys might help in the elucidation of the disease, or subcutaneous ones, or inoculations into the spleen. I think it also rather important that splenic anaemia (Bruhl's disease) should be closely investigated to see if it is due to the same parasite. Clinically, the diseases are identical, but I cannot find the original reference to see if those cases of Bruhl's had ever been abroad. In view of the recent remarkable observations by Schaudinn of the change of an intracorpuscular pigmented parasite into a trypanosome, we should, I think, consider the possibility of the Leishman-Donovan bodies having something to do with the resting stage of malaria. I do not say there is any evidence of this, but the gradual widening geographical distribution of this new disease shows that it is not limited to Assam, the home of kala-azar, but is common throughout other areas, many of which are intensely malarious.

XI.—JONATHAN HUTCHINSON, F.R.S.,
Consulting Surgeon, London Hospital.

MR. HUTCHINSON considered the fact that the Leishman-Donovan parasite had been found in Delhi sore was a discovery of considerable pathological value. He had always looked upon Delhi sore as being allied to lupus, and therefore possessing a tuberculous affinity. It, however, seemed possible that a true explanation of the disease had been found.

XII.—KENNETH MCLEOD, M.D.Edin., Colonel, I.M.S. (Retired).
Professor of Clinical and Military Medicine, Army Medical Staff College.

COLONEL MCLEOD observed that in the splenomegaly connected with the Leishman-Donovan body the haemorrhages seemed to be more severe and constant than in the cases of kala-azar in Assam.

XIII.—ALEXANDER CROMBIE, C.B., M.D.,
President of the Section.

THE PRESIDENT thought that the pigmentation so prevalent in cachexial fever might be due to the action of the Leishman-Donovan body and not to malaria. An observation that had come to his knowledge in this connexion might be of service in explaining the etiology of Oriental or Scinde sores and their connexion with trypanosomes or Leishman-Donovan bodies. It was well known that persons who attended upon or who drove camels were especially liable to a form of Oriental sore. The camel was the subject of trypanosomes, and an insect, the "camel fly," might prove to be the medium whereby man became infected from the camel and the production of the sores accounted for. There was a very close parallelism between the geographical distribution of camels and Oriental sore.

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spleen laundered with Giemsa's stain beneath me. Therefore I would urge blood examination before splenic puncture. A matter of great practical importance is the settlement of the way of exit and the way of entrance of the parasite. Its association with alimentary, glandular, and genital tracts, suggests that it emerges through alimentary and enters by buccal lesions. Oriental sore must now be regarded as a spleen disease, as sometimes leading to a general infection. Thus, I have seen a patient who suffered from oriental sore, and subsequently became the subject of disease of the testes, supposed to be tuberculous, for which he was castrated.

IX.—Dennis Brown, C.M.G.

(Colonial Hospital, Lagos, Colonial Surgeon.)

Colonel Bruce said I have disagreed with the greatest interest to Major Leishman's and the other papers on this interesting and apparently most important of diseases—kala-azar—and I think this Section may congratulate itself upon the important work which has been brought before it this morning. In fact, one of the most interesting of the experiments brought forward is that by Captain Rogers on the development of Leishman's bodies into trypanosomes—in vitro. The experiment was on the simplest lines. I understand he simply placed a few drops of infected spleen blood in a test tube and kept it at 22° C. In a short time beautiful fully developed trypanosomes were found to be present. It sounds like a fairy tale, and yet it is difficult to see where a fallacy could have crept in. He states he was working with sterilized apparatus. We know Rogers's organisms will sometimes develop from tsetse-fly. I hereby congratulate Captain Rogers on this startling observation, and await eagerly its confirmation. In the second place, I would like to call attention to the nomenclature of these bodies. Lately I find they called this Leishman-Donovan bodies, and usually they are called the Leishman-Donovan bodies. Now, as I understand this subject, this indicates observation of the presence of these bodies in the spleen of cases of kala-azar made by Leishman, and by Leishman alone. Donovan only confirmed the observation, as many others have done. It would be just as logical to call these bodies the Leishman-Donovan-Ross-Henry-Manson-Low, etc., bodies, as Leishman-Donovan. I do not suppose it is Donovan's fault that this honour has been thrust upon him, it is rather a case of being saved from our friends.

X.—G. C. Low, M.B.(Edin.),

Superintendent, Leeds School of Tropical Medicine.

Dr. Low said: In reply to Colonel Bruce's remarks on Captain Rogers's experiments on the production of trypanosomes from cultures of Leishman-Donovan bodies, I may state that, in the case Sir Patrick Manson and I described from the London School of Tropical Medicine, cultures were attempted. Tubes of haemoglobin agar and haemoglobin broth were inoculated with splenic blood and incubated, some at 22° C., others at room temperature. In neither of these did the parasites multiply, and on the second day had entirely disappeared. Similarly fresh spirochaetes, reared with vaccine and watched under the microscope for four days, showed no movements in the parasite and never at develop. ment. Our experiments, however, were, perhaps, too few to be considered in any way conclusive. In regard to the pathology of this disease, many of the previous speakers have used different terms as regards the cells of the body in which the parasites are found. I think it is important that the exact site should be thoroughly determined. They are found in the macrophages, or splenic cells of the spleen, in the reticulum cells of the liver, in the narrow cells, and also apparently in some situations in the endothelial cells. Experiments on monkeys might help in the determination of the disease, or whether one, or more organisms into the spleen. I think it also rather important that splenic anaemia (Banti's disease) should be closely investigated to see if it is due to the same parasite. Clinically the diseases are identical, but I cannot find the original evidence in one of those cases of Banti's had ever been stained. In view of the recent remarkable observations by Leishman on the change of an intracorpuscular parasite into a trypanosome, we should, I think, consider the possibility of the Leishman-Donovan bodies having something to do with the resting stage of malaria. I do not say there is any evidence of this, but the gradual widening geographical distribution of this new disease shows that it is not limited to Assam, the home of kala-azar, but is common throughout other areas, many of which are intensely malarious.

XI.—Leishman Donovan, F.R.S.

Consulting Pathologist, Indian Hospital.

Sir Leishman mentioned the fact that the Leishman-Donovan parasite had been found in leprous spleen was a discovery of considerable pathological value. He had always looked upon Delhi-sore as being allied to lupus, and therefore presenting a tuberculous affinity. It, however, seemed possible that a true explanation of the disease had been lost sight of.

XII.—Kenneth Mellon, M.D.(Edin.), Colonel, I.M.S.

(Retired)

Professor of Clinical and Military Medicine, Army Medical College.

Colonel Mellon said he observed that in the epidemiology connected with the Leishman-Donovan body the hemorrhagic element to be more severe and constant than in the cases of kala-azar in Assam.

XIII.—Malcolm Graham, C.B., M.D.,

President of the Section.

The President thought that the dissemination as presented in academical investigations due to the action of the Leishman-Donovan body and not to malaria. An observation that had come to his knowledge in this connection might be of service in explaining the etiology of Oriental or "white sore" and their connection with trypanosomes or Leishman-Donovan bodies. It was well known that persons who attended upon or who drove camels were especially liable to a form of Oriental sore. The camel was the subject of trypanosomes, and an insect, the "camel fly," might prove to be the medium whereby man became infected from the camel and the production of the sore accounted for. There was a very close parallelism between the geographical distribution of camels and Oriental sore.

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